Hidden energy flows in strongly coupled nonequilibrium systems

STEVEN J. LARGE(a) and DAVID A. SIVAK(b)

Department of Physics, Simon Fraser University - Burnaby, British Columbia, V5A 1S6, Canada

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Abstract – Quantifying the flow of energy within and through fluctuating nanoscale systems poses a significant challenge to understanding microscopic biological machines. A common approach involves coarse graining, which allows a simplified description of such systems. This has the side effect of inducing so-called hidden contributions (due to sub-resolution dynamics) that complicate the resulting thermodynamics. Here we develop a thermodynamically consistent theoretical framework describing the nonequilibrium excess power internal to autonomous systems, and introduce a phenomenological framework to quantify the hidden excess power associated with their operation. We confirm our theoretical predictions in numerical simulations of a minimal model for both a molecular transport motor and a rotary motor.

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Introduction. – The thermodynamic description of strongly fluctuating nanoscale systems has provided a mathematical framework in which to address some of the most fundamental physical aspects of microscopic biological systems [1]. Building upon general results like the fluctuation theorems [2–5], the ability to quantify dissipation in stochastic processes out of equilibrium has uncovered a number of theoretical results limiting the achievable performance of nonequilibrium systems. For instance, the thermodynamic uncertainty relation [6,7] and its generalizations [8–10] provide insight on many seemingly universal constraints faced by nonequilibrium systems [11–16].

Fundamentally, the consistency of stochastic thermodynamics relies on an assumption of timescale separation, allowing one to clearly distinguish the system from its surroundings [17–19]. Furthermore, in its most common forms, stochastic thermodynamics also assumes weak coupling between the system of interest and the environment. In microscopic biological systems, however, both assumptions are often violated. The separation of timescales becomes blurred as there are often a number of comparable timescales relevant to a given problem, and biomolecular systems often consist of multiple strongly interacting subsystems.

For instance, the molecular machine F_oF_1-ATP synthase (producing the majority of the cellular energy currency ATP) exhibits strong coupling between the passage of protons through the mitochondrial membrane, the mechanical rotation of a central crankshaft, and the production of ATP [20]. In fact, the chemical and mechanical aspects of the motor are inseparable from one another, both being necessary to understand the dynamics of the machine [21]. This strong coupling between chemical and mechanical processes is ubiquitous among molecular machines [22,23].

In practice, the description of such systems is often simplified through the use of a coarse-graining procedure, whereby the state space of the full mechnanochemical system is projected onto a smaller set of mesostates, each aggregating several (unresolvable) microstates [17]. Here, the observed dynamics of a molecular machine consists of large jumps, interleaved with small-scale fluctuations [24]. The large jumps are often taken to indicate a chemical reaction —producing an instantaneous change in the energy potential experienced by the molecular machine—and the full dynamics can then be mapped onto a discrete-state Markov jump model [1,25]. The observed chemical rates are then used to understand the thermodynamic properties (and functional capabilities) of the mechanochemical machine. However, such an approach by its very nature ignores so-called hidden contributions to thermodynamic quantities—such as internal energy flows—arising due to the mechanical dynamics at sub-mesostate resolutions [26]. Such internal energy flows play an important role in understanding the interactions between the
subcomponents of the molecular machine, and have been used to aid in identifying reaction coordinates in biomolecular dynamics [27].

Independent of such models, much research seeks to understand energy flows into nonequilibrium systems from a time-dependent external perturbation [28–30]. These efforts have largely been restricted to deterministic driving protocols—like those typically seen in single-molecule experiments [31–36]—but have recently been generalized to more closely parallel the in vivo dynamics of molecular machines [37–40]. However, as of yet, none of these control-theoretical approaches to quantifying energy flows within nanoscale nonequilibrium systems have fully appreciated the essential inter-system feedback that is necessary in fully autonomous systems [41–43].

In this article, we develop a thermodynamically complete phenomenological method for quantifying the hidden excess power within strongly coupled nonequilibrium systems. The hidden excess power represents an energy flow communicated between the components of a strongly coupled system, and unconstrained by the usual form of the second law—can become negative [41]. Such negative excess power is a signature of a fully autonomous Maxwell demon, achieving net flow of heat from the reservoir into a subsystem—where it is transduced into work—as a result of its strong coupling with another driven subsystem.

We find that the hidden excess work per chemical transition can be decomposed into two contributions, the timescale-separated (TSS) excess work (8)—the contribution to the excess work in the asymptotic TSS limit—and the nonequilibrium excess work, which is the additional contribution to the excess work when the mechanical states remain out of equilibrium at steady state. The hidden excess power (the excess work per chemical transition, averaged over the coarse-grained dynamics) is typically not easily calculable, as it requires information about hidden states. However, we provide a leading-order approximation of both the TSS excess work (11) and nonequilibrium excess work (12) which require only minimal information about the hidden-state dynamics. We demonstrate the utility of these approximations in two model systems, representing minimal models of linear and rotary mechanochemical molecular machines.

Coarse-grained representations of mechanochemical systems. — Molecular machines often couple mechanical motion to chemical reactions, for instance in kinesin [44] and F1-ATP synthase [45]. Thus their dynamics can be described by two coupled coordinates \( x \) and \( \lambda \), representing the state of mechanical and chemical subsystems [21,23]. Each chemical state \( \lambda \) induces a particular potential-energy landscape \( E(x | \lambda) \) on the mechanical subsystem such that, in the absence of any chemical changes, the mechanical subsystem relaxes to a conditional equilibrium distribution

\[
\pi(x | \lambda) = e^{-\beta E(x | \lambda)} + \beta F(\lambda),
\]

with \( \beta \equiv (k_B T)^{-1} \) the inverse temperature of the heat bath and \( F(\lambda) \equiv -\ln \int dx \exp(-\beta E(x | \lambda)) \) the conditional equilibrium free energy given the fixed chemical state \( \lambda \).

The chemical and mechanical subsystems evolve stochastically, with joint transition \( (\lambda_i, x') \rightarrow (\lambda_j, x) \) occurring at rate \( R_{ji}^{xx'} \). We further assume that the joint dynamics are bipartite, so that no simultaneous transitions in both \( x \) and \( \lambda \) occur. Thus \( R_{ji}^{xx'} = 0 \) when both \( j \neq i \) and \( x \neq x' \). Thermodynamically consistent mechanochemical dynamics—relaxing to the correct equilibrium distribution in the absence of any chemical driving (though producing nonequilibrium dynamics for nonzero chemical driving)—require that the chemical transition rates satisfy generalized detailed balance [46,47],

\[
\frac{R_{ji}^{x}}{R_{ji}^{x'}} = e^{-\beta \Delta G_{ji}(x)},
\]

where \( R_{ji}^{x} \equiv R_{ji}^{x,x} \) indicates the rate of chemical transition \( \lambda_i \rightarrow \lambda_j \) at fixed mechanical state \( x \), \( \Delta G_{ji}(x) = \Delta \mu_{ji} + \Delta E_{ji}(x) \) is the change in free energy during transition \( \lambda_i \rightarrow \lambda_j \), with \( \Delta \mu_{ji} \) and \( \Delta E_{ji}(x) \equiv E(x | \lambda_j) - E(x | \lambda_i) \) the associated respective changes in chemical potential and microstate energy for the transition \( \lambda_i \rightarrow \lambda_j \).

We consider transition rates obeying (2) of the general form

\[
R_{ji}^{x} = \Gamma_{\text{chem}} \exp \left\{ \frac{1}{2} \beta \left[ \Delta \mu_{ji} + E(x | \lambda_j) - E(x | \lambda_i) \right] \right\},
\]

where \( \Gamma_{\text{chem}} \) is a kinetic prefactor (with dimensions of inverse time) that quantifies the bare rate of chemical transitions in the absence of any differences in energy or chemical potential between states. We view the chemical dynamics as a coarse-grained representation of the mechanochemical system by defining coarse-grained states (mesostates) that aggregate all mechanical states at a given chemical state \( \lambda_i \), and their corresponding coarse-grained transition rates \( V_{ji}(t) \equiv \int R_{ji}^{x} \delta(x | \lambda_j) dx \), for conditional probability \( p(x, t | \lambda_i) \) over mechanical states within a given mesostate [17] (see sect. I in the Supplementary Material Supplementarymaterial.pdf (SM)) \( V_{ji}(t) \) is generally time-dependent due to the conditional microstate distribution \( p(x, t | \lambda_i) \), but is time-independent when the mechanical dynamics are at steady state.

In the TSS limit, where at steady state the conditional distribution \( p(x | \lambda) \) of mechanical states is the conditional equilibrium distribution \( \pi(x | \lambda) \) (1), the dissipation (entropy production) of the joint system is fully determined by the coarse-grained dynamics [17]. However, even in this limit, there are internal flows of energy and information between the mechanical and chemical subsystems [41].

Hidden excess work in molecular machines. — Here, we provide a method to quantify the hidden contributions to the excess power in a coarse-grained system, by
viewing the hidden mechanical subsystem as being driven by the stochastic chemical dynamics.

The flow of energy between the chemical and mechanical subsystems can be quantified by the average work

$$\langle \beta W_{\text{TSS}} \rangle_{ji} = \beta \int \Delta F_{ji}(x) p_{ji}^{\text{sw}}(x) \, dx$$

(4)
done on the mechanical subsystem by the chemical dynamics during transition $\lambda_i \rightarrow \lambda_j$. The average is over the switching-position distribution $p_{ji}^{\text{sw}}(x)$ of mechanical states $x$ from which the chemical transition $\lambda_i \rightarrow \lambda_j$ occurs [41], which in general depends on the dynamics of both the chemical and mechanical subsystems.

The average excess work is $\langle \beta W_{\text{ex}} \rangle_{ji} \equiv \langle \beta W_{\text{ex}} \rangle_{ji} - \beta \Delta F_{ji}$, for change $\Delta F_{ji} \equiv F(\lambda_j) - F(\lambda_i)$ in conditional equilibrium free energy upon the chemical transition. At steady state, the average rate of excess work (the excess power) on the mechanical subsystem is expressed in terms of coarse-grained rates as

$$\langle \beta P_{\text{ex}} \rangle_{\Lambda \rightarrow X} = \sum_{i,j} P_i V_{ji} \langle \beta W_{\text{ex}} \rangle_{ji}.$$  

(5)

$P_i$ is the probability of the mesostate with chemical state $\lambda_i$, and angle brackets $\langle \cdots \rangle_{\Lambda \rightarrow X}$ indicate an average over the dynamics of the chemical subsystem $\Lambda$ and mechanical subsystem $X$.

Motivated by the approach to discrete control protocols in ref. [38], we decompose the average excess work for transition $\lambda_i \rightarrow \lambda_j$ into two components,

$$\langle \beta W_{\text{ex}} \rangle_{ji} = \langle \beta W_{\text{ex}}^{\text{TSS}} \rangle_{ji} + \langle \beta W_{\text{ex}}^{\text{neq}} \rangle_{ji},$$

(6)

where $\langle \beta W_{\text{ex}}^{\text{TSS}} \rangle_{ji}$ is the excess work in the timescale-separated (TSS) limit where the mechanical subsystem fully equilibrates between chemical reactions —but still evolves slowly when compared with the environmental degrees of freedom, so that the reservoirs can still be clearly thermodynamically distinguished from the system— and $\langle \beta W_{\text{ex}}^{\text{neq}} \rangle_{ji}$ is the nonequilibrium excess work quantifying the additional work beyond the TSS work due to the mechanical subsystem being out of equilibrium.

**TSS excess work.** For the transition rates in (3), the timescale-separated switching-position distribution is the normalized geometric mean of the conditional equilibrium distributions at $\lambda_i$ and $\lambda_j$,

$$p_{ji}^{\text{sw}}(x) = \sqrt{\pi_i(x) \pi_j(x)},$$

(7)

where $\pi_i(x) \equiv \pi(x | \lambda_i)$, and $Z_{ji}^{\text{sw}} \equiv \int \sqrt{\pi_i(x) \pi_j(x)} \, dx$ normalizes the distribution. In information theory, $Z_{ji}^{\text{sw}}$ is the Bhattacharyya coefficient [48], a measure of the difference between two probability distributions. Inserting (7) into (4) and subtracting the free energy difference $\Delta F_{ji}$ gives an exact relation for the TSS excess work (see SM, sect. II)

$$\langle \beta W_{\text{ex}}^{\text{TSS}} \rangle_{ji} = \frac{1}{Z_{ji}^{\text{sw}}} \int \sqrt{\pi_i(x) \pi_j(x)} \ln \frac{\pi_i(x)}{\pi_j(x)} \, dx$$

(8a)

$$= D(\sqrt{\pi_i(x) \pi_j(x)} | | \pi_i) - D(\sqrt{\pi_i(x) \pi_j(x)} | | \pi_j),$$

(8b)

for relative entropy $D(p || q) \equiv \int p(x) \ln \frac{p(x)}{q(x)} \, dx$ between two distributions [49]. Intuitively, the TSS excess work quantifies the increase in additional free energy of the switching-position distribution $p_{ji}^{\text{sw}}(x)$ through the chemical reaction $\lambda_i \rightarrow \lambda_j$ [50]. (Equation (8b) was also derived for master-equation dynamics for a general switching-position distribution in [41].)

The TSS excess work is antisymmetric under index exchange, $\langle \beta W_{\text{ex}}^{\text{TSS}} \rangle_{ji} = - \langle \beta W_{\text{ex}}^{\text{TSS}} \rangle_{ij}$, and thus the TSS excess power (5) (obtained by averaging the transition-specific excess work over coarse-grained dynamics) is

$$\langle \beta P_{\text{ex}}^{\text{TSS}} \rangle_{\Lambda \rightarrow X} = \sum_{i<j} (P_i V_{ji} - P_j V_{ij}) \langle \beta W_{\text{ex}}^{\text{TSS}} \rangle_{ji}. $$

(9)

Thus, even for nonzero $\langle \beta W_{\text{ex}}^{\text{TSS}} \rangle_{ji}$ for the chemical transition $\lambda_i \rightarrow \lambda_j$, the associated hidden power averaged over transitions in each direction vanishes when there is no net chemical flux ($P_i V_{ji} = P_j V_{ij}$). This occurs, for instance, when there is no chemical driving ($\Delta \mu = 0$), and is a direct result of the autonomous nature of the system, exemplifying the essential importance of requiring the rates (3) to satisfy local detailed balance (2).

The TSS excess work further simplifies in the small-$\Delta \Lambda$ limit, where Taylor expanding (8a) produces (see SM, sect. III)

$$\langle \beta W_{\text{ex}}^{\text{TSS}} \rangle_{ji} = \frac{1}{4!} \Delta \lambda_{ji}^k \delta f_m(\lambda_i) \Delta \lambda_{ji}^m \Delta \lambda_{ji}^f \Delta \lambda_{ji}^k,$$

(10)

where $\Delta \lambda_{ji}^k$ is the change in the $k$-th component of the chemical state vector $\lambda_i$ during the transition $\lambda_i \rightarrow \lambda_j$, and the rank-3 tensor

$$S_{mk}(\lambda) = \langle \delta f_m \delta f_k \delta f_k \rangle_{\lambda},$$

(11)

is the third centered moment of conjugate forces $f_k \equiv -\partial \mu/k B(x | \lambda)$. Here, we use an Einstein summation notation, where repeated indices are implicitly summed over. In contrast, the analogous infinite-time excess work in [38] is second order in $\Delta \Lambda$ and uses the force variance $\langle \delta f_m \delta f_k \rangle_{\lambda}$ instead of the third centered moment. Here, the feedback of the mechanical subsystem on the chemical dynamics results in cancellation of the second-order terms.

**Nonequilibrium excess work.** In the small-$\Delta \Lambda$ limit, linear-response theory provides a simple approximation for the nonequilibrium excess work $\langle \beta W_{\text{ex}}^{\text{neq}} \rangle_{ji}$. In particular, if upon the chemical transition $\lambda_i \rightarrow \lambda_j$, the corresponding change in the mechanical energy landscape $E(x | \lambda_i) \rightarrow E(x | \lambda_j)$ is small, $E(x | \lambda_j)$ is well approximated by a first-order Taylor expansion about $\lambda_i$. We
additionally assume a moderate timescale separation between the mechanical and chemical dynamics, such that the relaxation time of the conjugate forces $f_k$ is significantly shorter than the chemical-state dwell time. This constraint is weaker than the timescale-separation limit typically considered in coarse graining, where the hidden states are assumed to relax infinitely faster than the chemical dynamics and thus equilibrate fully [17].

Under these assumptions, the leading-order contribution to the nonequilibrium excess work during chemical transition $\lambda_i \rightarrow \lambda_j$ is (see SM, sect. IV)

$$\langle \beta W_{\text{ex}}^\text{neq} \rangle_{ji} \approx \beta \Gamma_{ji} \zeta_{kk}^{\lambda_i} \Delta \lambda_{ji} \frac{\sum_i P_i V_{ij} \Delta \lambda_{ji}^c}{V_{ii}}.$$ (12)

$$\Gamma_{ji} \equiv \Gamma_{\text{chem}} \exp\left(-\frac{1}{2} \beta \Delta \mu_{ji}\right), \quad V_{ii} \equiv \sum_i P_i V_{is} \text{ is the total rate of chemical transitions entering } \lambda_i, \text{ and the summation index } s \text{ runs over all chemical states. } \zeta_{kk}^{\lambda_i}(\lambda) \equiv \beta \int_0^\infty \left(\delta f_k(0) \delta f_k(t)\right)_{\lambda} \, dt \text{ is the generalized friction tensor} \text{[30]} \text{ that quantifies the leading-order dissipation due to nonequilibrium driving by a deterministic control protocol. Equation (12) quantifies the nonequilibrium excess work using information about the coarse-grained dynamics and the friction tensor } \zeta_{kk}^{\lambda_i}(\lambda), \text{ which is determined from the hidden states' equilibrium fluctuations.}

At steady state, the excess power by the chemical dynamics on the mechanical subsystem averages over the coarse-grained transitions,

$$\langle \beta P_{\text{ex}} \rangle_{\lambda \rightarrow \lambda} = \sum_{i,j} V_{ji} \left[ \langle \beta W_{\text{ex}}^\text{TSS} \rangle_{ji} + \langle \beta W_{\text{ex}}^\text{neq} \rangle_{ji} \right].$$ (13)

The near-equilibrium expressions for the TSS (8) and nonequilibrium excess work (12) in terms of conditional equilibrium averages permits estimation of the excess power in experimental investigation of autonomous mechanochemical molecular machines: the low-resolution observations of hidden-state fluctuations it requires are more tractable than inferring the full mechanochemical dynamics of the motor [51,52].

**Model systems.** We illustrate our theoretical predictions by investigating the hidden excess power in two model systems, representing linear-transport and rotary molecular motors. In both cases, the chemical coordinate evolves on a discrete, one-dimensional lattice, with only nearest-neighbor transitions having rates given by (3). The mechanical coordinate $x$ (in the rotary model) diffuses in a one-dimensional energy landscape $E(x \mid \lambda)$ determined by the instantaneous chemical state $\lambda$. Figure 1 shows a schematic of both model systems.

In the linear-transport motor, the TSS excess work (8) is zero, thus serving as a model to isolate the nonequilibrium excess work (12). Conversely, for the rotary motor we analyze its excess work in the TSS limit where the nonequilibrium excess work is zero, thereby isolating the effects of the TSS excess work (8).

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![Fig. 1: Schematic of model mechanochemical machines.](image)

(a) Chemical reaction diagram, an infinite one-dimensional lattice of chemical states. (b), (c): conditional energy landscapes for (b) linear $E(x \mid \lambda)$ and (c) rotary $E(\theta \mid \lambda)$ models. (d), (e): equilibrium distribution (black) and forward/reverse equilibrium switching-position distributions (solid green/orange) for $\lambda_i$ blue state in (b), (c)) for (d) linear and (e) rotary models. Dashed curves in (d) indicate nonequilibrium switching-position distributions for net chemical flux towards higher-index $\lambda$ (to the right in (a)).

**Linear-transport motor.** The linear-transport motor has a one-dimensional mechanical degree of freedom subject to a harmonic potential $E(x \mid \lambda_i) = \frac{1}{2} k_{\text{trap}} (x - \lambda_i)^2$, with the instantaneous chemical state $\lambda_i$ determining the potential minimum. Figure 1(a), (b) shows a schematic.

The equilibrium mechanical distributions for consecutive chemical states are only distinguished by their mean $\lambda_i$, so we observe the system in a comoving frame by changing mechanical coordinate to the relative position $x - \lambda_i$. This reference frame has a steady-state distribution for time-independent transition rates (3) and uniform fixed $\Delta \mu_{i+1,j} = \Delta \mu < 0$ biasing the machine to (on average) move forward. Here, the generalized friction is uniform and equals the viscous friction, $\zeta = \gamma$, and the steady-state coarse-grained forward and reverse rates $V_{\pm}$ and probabilities $P_i$ are uniform. Equation (12) approximates the steady-state nonequilibrium excess work, simplifying in this case to (see SM, sect. IV)

$$\langle \beta W_{\text{ex}}^\text{neq} \rangle_{\Delta \lambda} \approx \beta \xi \Delta \lambda^2 \frac{(V_+ - V_-) (V_+ \Gamma_+ - V_- \Gamma_-)}{(V_+ + V_-)^2}.$$ (14)

Here, the nonequilibrium excess work depends on the chemical driving $\Delta \mu$ through both the coarse-grained chemical rates $V_{\pm} \propto \exp(\pm \frac{1}{2} \beta \Delta \mu)$ (following from their dependence on microscopic transition rates $R_{\pm}$ and (3)).
Hidden energy flows in strongly coupled nonequilibrium systems

and the energy-independent rate $\Gamma_\pm \propto \exp(\pm \frac{1}{2} \beta \Delta \mu)$. Figure 2 compares the theoretical predictions (14) with numerical results, showing agreement in the small-$\Delta \lambda$ limit.

**Rotary motor.** Next, we consider the Kawaguchi-Sasa-Sagawa (KSS) model of F$_1$-ATPase [45]. Here, the rotational angle $\theta$ of F$_1$-ATPase’s crankshaft evolves in the potential of mean force (PMF)

$$\beta E_{\text{KSS}}(\theta | \lambda_i) = \frac{1}{2} \beta k_c (\theta - \lambda_i)^2 - \ln \left[ e^{-\beta k_c (\theta - \lambda_i)} + e^{\beta \Delta E_S + \frac{1}{2} \beta k_c \phi^2} \right],$$

(15)

arising from fast switching between two harmonic potentials, each with stiffness $k_c$, with angular offset $\phi$ and energetic offset $\Delta E_S$. Figure 1(a), (c) shows a schematic. Unlike the (purely harmonic) linear-transport model (in the previous subsection), for $\Delta E_S \neq 0$ and $\phi \neq 0$ this potential is asymmetric in $\theta$, generally producing nonzero TSS excess work (8b). To isolate the effects of the nonzero TSS excess work, we consider this model in the TSS limit, where the mechanical subsystem comes to conditional equilibrium between each chemical transition, and the nonequilibrium excess work (12) vanishes.

Figure 3 compares the exact TSS excess work $\langle \beta W_{\text{TSS}}^{\text{TSS}} \rangle_{\text{FW}} \equiv \langle \beta W_{\text{TSS}}^{\text{TSS}} \rangle_{\text{FW}} / \max \Delta E_S / \langle \beta W_{\text{TSS}} \rangle_{\text{FW}}$ per forward step, as a function of energy offset $\Delta E_S$ (nondimensionalized by the angular offset between minima), for several chemical step sizes $\Delta \lambda^* = \Delta \lambda / \phi$ (columns) and spring constants $\beta k_c$ (rows). Colored solid curves: exact; dashed curves: small-$\Delta \lambda$ approximation (10).

with the exact calculation (8). For large step sizes and stronger spring constants, the approximation in (10) begins to break down.

At the level of the (driven) mechanical subsystem, negative TSS excess work indicates net heat flow from the thermal reservoir into the mechanical subsystem and onward as work extracted by the chemical dynamics. The strong coupling between mechanical and chemical subsystems ensures thermodynamic consistency by a compensating heat flow from the chemical subsystem to the thermal reservoir that rescues what would otherwise be a violation of the second law [42,43]. In such circumstances, the chemical dynamics operate as a fully autonomous Maxwell demon, effectively using the information gleaned through strong coupling to the mechanical subsystem to transduce heat from the bath into extracted work.

**Discussion.** In this article, we present a phenomenological formalism to estimate the hidden excess power internal to coarse-grained autonomous nonequilibrium systems, which only requires the coarse-grained chemical dynamics and minimal information about the hidden mechanical dynamics. This theoretical framework provides a means to estimate the hidden energy flows within molecular machines without explicitly modeling their microscopic dynamics.

We identify two distinct contributions to the hidden excess work: the TSS excess work (8) —which persists in the TSS limit, when between chemical reactions the hidden mechanical subsystem fully relaxes to a conditional equilibrium— and the nonequilibrium excess work (12),

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which is the additional energetic cost due to the mechanical subsystem being out of equilibrium.

The exact TSS excess work \( \langle \beta P_{\text{ex}} \rangle_{\lambda} \) for a particular chemical transition is the difference between two relative entropies (8), and can be interpreted as quantifying the concomitant change of the additional free energy in the mechanical subsystem [41]. Unlike the analogous infinite-time excess work in [38], the TSS excess work for any particular transition can be either positive or negative. This is consistent with findings in ref. [41], where we showed that — due to the strong coupling between the mechanical and chemical subsystems — the excess power \( \langle \beta P_{\text{ex}} \rangle_{\lambda} \) (the rate of excess work, averaged over all coarse-grained transitions) is not, in itself, constrained by the second law, and thus can become negative.

We also identify a phenomenological expression that approximates (to leading order in \( \Delta \lambda \)) the TSS work of the chemical dynamics on the mechanical system by the third centered moment of the conditional equilibrium distribution of conjugate forces (11). This is in contrast to a similar expansion of the infinite-time excess work in [38] that is second order in \( \Delta \lambda \) and uses the force variance in place of the third moment in (11). Here, feedback from the mechanical subsystem to the chemical dynamics leads to exact cancellation of terms that are second order in \( \Delta \lambda \). Additionally, in the moderate timescale-separated limit, the nonequilibrium excess work is determined by the generalized friction tensor (12), which can be inferred through observations of equilibrium force fluctuations.

While this decomposition of the average excess work per transition is reminiscent of the adiabatic/nonadiabatic decomposition of the entropy production [53], the individual terms in (6) bear no direct relationship with either contribution to the entropy production; moreover, the excess work internal to such autonomous systems is not directly related to entropy production [41].

Our theoretical framework can be used as a tool in experimental studies of molecular machines to better understand excess power in autonomous systems and address how internal energy flows influence whole-system function. In particular, recent experiments on kinesin [51] and F1 ATPase [52] have used their mechanical fluctuations to infer hidden entropy production; our theoretical framework can make use of these measurements of mechanical fluctuations to approximate both the TSS excess work and nonequilibrium excess work.

Furthermore, the identification of negative steady-state excess power has an interesting physical interpretation, providing a signature of Maxwell-demon behavior in the mechanochemical machine [42]. Specifically, negative excess power means that, on average, there is net heat flow from the reservoir into the subsystem being driven. We showed an example of this with the TSS excess work in the rotary model system, and analogous behavior was recently found in a similar bistable potential in ref. [41]. Our framework provides a tractable method to measure this quantity, and can be used to identify such information-thermodynamic features in biological molecular machines.

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