Stochastic control in microscopic nonequilibrium systems

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Abstract – Quantifying energy flows at nanometer scales promises to guide future research in a variety of disciplines, from microscopic control and manipulation, to autonomously operating molecular machines. A general understanding of the thermodynamic costs of nonequilibrium processes would illuminate the design principles for energetically efficient microscopic machines. Considerable effort has gone into finding and classifying the deterministic control protocols that drive a system rapidly between states at minimum energetic cost. But when the nonequilibrium driving is imposed by a molecular machine that is itself strongly fluctuating, driving protocols are stochastic. Here we generalize a linear-response framework to incorporate such protocol variability and find a lower bound on the work that is realized at finite protocol duration, far from the quasistatic limit. Our findings are confirmed in model systems. This theory provides a thermodynamic rationale for rapid operation, independent of functional incentives.

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Introduction. – In the past two decades, significant strides have been made in uncovering the physics of nonequilibrium processes [1,2]. The fluctuation theorems, for instance, place stringent constraints on the behavior of physical systems even far from equilibrium [3–8]. Complementary to theoretical progress, the development of a multitude of experimental techniques to probe the microscopic physics of fluctuating systems has led to the direct verification of these strikingly general descriptions of the fluctuations and dissipation in physical systems [9–13].

While the fluctuation theorems characterize general properties of thermodynamic systems, they do not directly address questions of optimality. For instance, there is great interest in studying the efficiency of driven nonequilibrium systems, toward the goal of understanding the physical limits of biomolecular processes, perhaps pointing to design principles [14]. A paradigmatic model system is the F0,F1 ATP synthase rotary motor, which uses rapid (presumably far-from-equilibrium) mechanical rotation of a crankshaft — itself driven by proton flow across a membrane — to drive synthesis of ATP molecules [15]. We hypothesize that evolution has placed selective pressure on the development of energetically efficient machinery [16], which suggests that uncovering general features of efficient nonequilibrium driving may shed light on the fundamental principles underlying the design of microscopic machines. Better understanding of such biomolecular machines promises practical benefits ranging from the de novo construction of synthetic motors for next-generation nanomedicine [17] to a better understanding of diseases related to cellular transport, such as ALS and Alzheimer’s [18].

To address these questions, we adopt a framework quantifying the nonequilibrium efficiency of time-dependent driving protocols connecting the initial and final system macrostates [19]. This formalism has been applied to a number of model thermodynamic systems [20–23], and promises to inform the design of future single-molecule experiments on biophysical systems [24].

Efforts in this area have focused on deterministic protocols in experimental paradigms such as flipping or erasing a classical bit [25], or manipulating a biomacromolecule using optical traps or atomic force microscopy [20]. A deterministic protocol lends itself naturally to single-molecule experiments, where the same time-dependent driving protocol can be reliably repeated. Yet in biomolecular contexts, the nonequilibrium driving may be imposed by molecular machines that are composed of protein...
components. At ambient temperature, these soft-matter system components (such as the crankshaft of ATP synthase) undergo strong conformational fluctuations, hence system components (such as the crankshaft of ATP synthesis) are soft-matter components. At ambient temperature, these soft-matter systems create an additional energetic cost associated with slow control parameter velocity fluctuations, this implies a minimal cost for stochastic control—the only control modality available for living soft-matter systems.

**Theoretical background.** We consider a system in contact with a heat bath at temperature $T$, with equilibrium distribution

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

over microstates $x$ with energy $E(x,\lambda)$ given experimentally controlled parameters $\lambda$. Here $F(\lambda)$ is the equilibrium free energy and $\beta \equiv (k_B T)^{-1}$ the inverse temperature. A control protocol $\lambda$: $\lambda_i \rightarrow \lambda_f$ is a schedule of changing the control parameters $\lambda(t)$ from an initial $\lambda_i$ at $t = 0$ to a final $\lambda_f$ at time $\tau$. $W_{\text{ex}} \equiv W - \Delta F$ is the excess work expended in performing protocol $\lambda$, i.e., the work required above and beyond the equilibrium free energy change $\Delta F$.

Within the linear-response regime, the excess power at time $t$ in a given control protocol $\lambda_f$, averaged over system responses, takes on the integral expression [19]

$$
\langle P_{\text{ex}}^\lambda \rangle_{\lambda_f} = \dot{\lambda}^i(t) \int_{-\infty}^t \langle \delta f_i(0) \delta f_j(t - t') \rangle_{\lambda(t)} \dot{\lambda}^j(t') \, dt',
$$

where $\dot{\lambda}^i = d\lambda^i/dt$ denotes differentiation with respect to time, angled brackets $\langle \cdots \rangle_{\lambda_f}$ indicate an instantaneous average at time $t$ over system responses to protocol $\lambda$, angled brackets $\langle \cdots \rangle_{\lambda(t)}$ indicate an average over equilibrium fluctuations at fixed control parameters $\lambda(t)$, and $f_i \equiv -\partial_i E$ is the generalized force conjugate to the $i$-th control parameter. Throughout we employ the Einstein summation notation, implicitly summing over any repeated indices.

If the control protocol $\Lambda$ is sufficiently smooth, such that

$$
\dot{\lambda}^i(t) \gg (t' - t) \dot{\lambda}^i(t),
$$

for time separations $t' - t$ over which the conjugate force autocorrelation $\langle \delta f_i(0) \delta f_j(t - t') \rangle_{\lambda(t)}$ is significantly greater than zero, then the $j$-th control parameter velocity in (2) can be approximated by its current value, $\dot{\lambda}^j(t') \approx \dot{\lambda}^j(t)$, and the excess power becomes

$$
\langle P_{\text{ex}}^\lambda \rangle_{\lambda_f} = \dot{\lambda}^i \zeta_{ij}(\lambda) \dot{\lambda}^j.
$$

In what follows, for notational convenience we suppress the explicit time dependence of $\dot{\lambda}^i$ (see the Supplementary material SupplementaryMaterial.pdf (SM), sect. V, for more details).

$\zeta_{ij}(\lambda)$ is a generalized friction tensor on the space of control parameters,

$$
\zeta_{ij}(\lambda) \equiv \beta \int_0^\infty \langle \delta f_i(0) \delta f_j(t) \rangle_{\lambda} \, dt = \beta \tau_{ij}^R \langle \delta f_i \delta f_j \rangle_{\lambda},
$$

where $\tau_{ij}^R$ is the integral relaxation time [26], and $\langle \delta f_i \delta f_j \rangle_{\lambda}$ is the equilibrium force variance [19]. Under linear response, the excess work is

$$
\langle W_{\text{ex}}^\lambda \rangle_{\lambda_f} = \int_0^\tau \langle P_{\text{ex}}^\lambda \rangle_{\lambda_f} \, dt \approx \int_0^\tau \dot{\lambda}^i \zeta_{ij}(\lambda) \dot{\lambda}^j \, dt,
$$

for duration $\tau$ of the control protocol $\Lambda$.

The generalized friction tensor $\zeta_{ij}(\lambda)$ also provides a measure of thermodynamic length $[27]

$$
L(\lambda) \equiv \int_0^\tau \sqrt{\dot{\lambda}^i \zeta_{ij}(\lambda) \dot{\lambda}^j} \, dt,
$$

along a protocol $\lambda$. For a given path in control parameter space connecting $\lambda_i$ to $\lambda_f$, the thermodynamic length is independent of the protocol duration $\tau$, and through a Cauchy-Schwarz inequality provides a lower bound on the excess work, $\langle W_{\text{ex}}^\lambda \rangle_{\lambda_f} \geq L(\lambda)^2/\tau$. This bound is saturated for a given duration $\tau$ when the protocol follows the geodesic curve connecting $\lambda_i$ to $\lambda_f$ [27–34].

**Protocol ensembles and stochastic control.** Here, instead of a single protocol $\lambda$: $\lambda_i \rightarrow \lambda_f$, we consider an ensemble $\Omega$ of protocols, where each protocol $\Lambda$ satisfies (3) and occurs with probability $P[\Lambda|\Omega]$. The excess power $\langle P_{\text{ex}}^\lambda \rangle_{\lambda_f}$ at time $t$ during protocol $\Lambda \in \Omega$, averaged over system fluctuations, is now a random variable (4) since $\lambda^i$, $\zeta_{ij}(\lambda)$, and $\dot{\lambda}^j$ are all functions of the random protocol $\Lambda$. The excess power, averaged over system and protocol fluctuations, is

$$
\langle P_{\text{ex}}^\lambda \rangle_{\lambda_f} \equiv \int \langle P_{\text{ex}}^\lambda \rangle_{\lambda_f} P[\Lambda|\Omega] \, D[\Lambda],
$$

where the integral is taken over all protocols and hence all instantaneous values of $\lambda(t)$, $\langle \cdots \rangle_{\Omega}$ indicate an average over the instantaneous distribution of control parameter.
positions or velocities at time $t$ due to the protocol ensemble $\Omega$.

When the ensemble is tightly localized around the average protocol, such that the friction varies little over control parameter values with significant support, the excess power (averaged over protocol and system fluctuations) is well approximated by expanding $\langle P_{ex}\rangle_{\Lambda_{opt}}$, (4) about the mean values of its arguments $\dot{\lambda}$, $\ddot{\lambda}$, and $\zeta_{ij}(\lambda)$ [35]:

$$\langle P_{ex}\rangle_{\Omega} \approx \langle \dot{\lambda} \rangle_{\Omega} \zeta_{ij}(\lambda) \langle \ddot{\lambda} \rangle_{\Omega} + \zeta_{ij}(\lambda) \langle \delta \dot{\lambda} \delta \dot{\lambda} \rangle_{\Omega}.$$  \(9\)

The SM, sect. I, gives a full derivation using a weak-noise perturbation expansion.

Time integration of (9) gives the average excess work required to perform a random protocol sampled from $\Omega$,

$$\langle W_{ex}\rangle_{\Omega} = \int_{0}^{\tau} \left[ \langle \dot{\lambda} \rangle_{\Omega} \zeta_{ij}(\lambda) \langle \ddot{\lambda} \rangle_{\Omega} + \zeta_{ij}(\lambda) \langle \delta \dot{\lambda} \delta \dot{\lambda} \rangle_{\Omega} \right] dt,$$  \(10\)

where $\langle \cdots \rangle_{\Omega}$ indicates an average over all protocols $\Lambda \in \Omega$, weighted by $P[\Lambda|\Omega]$. The first RHS term resembles (6), quantifying the cost associated with fast operation, while the second term quantifies the energetic cost resulting from variability in the protocol velocities. Both terms are integrated along the (deterministic) average protocol specified by the average velocity $\langle \dot{\lambda} \rangle_{\Omega}$. Thus, in the weak protocol-noise limit the effect of variable control only depends on the friction along this average path and the variation in velocities as a function of time.

**Lower bound on excess work.** The Cauchy-Schwarz inequality gives a lower bound for the first RHS term in (10) involving the thermodynamic length $L(\langle \lambda \rangle_{\Omega})$ between the initial and final states of the average protocol $\langle \lambda \rangle_{\Omega}$ [27], leading to a lower bound on the excess work achieved at a finite protocol duration $\tau$,

$$\langle W_{ex}\rangle_{\Omega} \geq \frac{L(\langle \lambda \rangle_{\Omega})^{2}}{\tau} + \frac{\langle \zeta_{ij}(\langle \lambda \rangle_{\Omega}) \langle \delta \dot{\lambda} \delta \dot{\lambda} \rangle_{\Omega} \rangle_{\Omega}}{\tau},$$  \(11\)

where we write the average of an instantaneous quantity over the protocol ensemble as $\langle \cdots \rangle_{\Omega} \equiv \tau^{-1} \int_{0}^{\tau} \cdots dt$.

This lower bound represents a tradeoff between the first RHS term quantifying the energetic costs associated with pushing a system out of equilibrium (scaling as $\tau^{-1}$ with protocol duration) and the second term quantifying the average contribution of protocol fluctuations to excess work, which increases with $\tau$ if $\zeta_{ij}(\lambda)$ is positive definite (assumed in what follows).

If the control parameter velocity variance is independent of the average velocity, this lower bound is minimized at a finite protocol duration

$$\tau_{opt} = \frac{L(\langle \lambda \rangle_{\Omega})}{\langle \zeta_{ij}(\langle \lambda \rangle_{\Omega}) \langle \delta \dot{\lambda} \delta \dot{\lambda} \rangle_{\Omega} \rangle_{\Omega}}^{1/2},$$  \(12\)

revealing a fundamental lower bound on the excess work,

$$\langle W_{ex} \rangle_{\Omega} \geq 2\langle \zeta_{ij}(\langle \lambda \rangle_{\Omega}) \rangle_{\Omega}^{1/2} L(\langle \lambda \rangle_{\Omega}).$$  \(13\)

This lower bound is saturated when the average protocol $\langle \lambda \rangle_{\Omega}$ follows the geodesic from $\lambda_i$ to $\lambda_j$ (similar to the deterministic case). The existence of a lower bound on work realized at finite protocol duration constitutes our main result. In the linear-response regime, the lower bound and optimal protocol duration take on the simple forms in (13) and (12), respectively.

For a single control parameter, (13) and (12) can be recast solely in terms of intensive quantities as a lower bound on the average excess force $\langle f_{ex}\rangle_{\Omega} \equiv \langle W_{ex}\rangle_{\Omega}/\Delta \lambda$ produced by an optimal mean control parameter velocity $\langle \dot{\lambda} \rangle_{\Omega}^{opt} \equiv \Delta \lambda/\tau_{opt}$. When the friction and control parameter velocity variance are both uniform, the excess force bound and optimal velocity simplify to

$$\langle \dot{\lambda} \rangle_{\Omega}^{opt} = \sqrt{\langle \delta \dot{\lambda} \delta \dot{\lambda} \rangle_{\Omega}},$$  \(14a\)

$$\langle f_{ex}\rangle_{\Omega} \geq 2\zeta(\langle \dot{\lambda} \rangle_{\Omega}^{opt}).$$  \(14b\)

The optimal mean velocity is the root-mean-squared control parameter velocity fluctuations, producing a mean excess force equal to twice the Stokes drag on the control parameter when moving at the optimal mean velocity through the “viscous” control parameter space subject to generalized friction coefficient $\zeta$.

In the specific case in which across the entire protocol the integral relaxation time is constant and equals $\tau = (\beta \langle \zeta_{ij}(\langle \lambda \rangle_{\Omega}) \langle \delta \dot{\lambda} \delta \dot{\lambda} \rangle_{\Omega} \rangle_{\Omega})^{-1}$, our lower bound (13) reduces to Machta’s bound on entropy production of a stochastically driven process [36]. This equality is achieved in the one-dimensional drift-diffusion process considered by Machta when protocol fluctuations come from the interaction of the control parameter with a thermal reservoir at the same temperature as the reservoir producing system fluctuations. Thus, our derived lower bound (13) generalizes Machta’s bound to systems with variable integral relaxation times and arbitrary fluctuations of the control parameter. The SM, sect. II, gives more details.

**Model ensembles.** We illustrate our theoretical approximation (11) using two model protocol ensembles. In each case, the system is a Brownian particle with unit mass evolving according to an overdamped Langevin equation on a one-dimensional potential. Driving forces are produced by a harmonic potential $U(x, \lambda) = \frac{1}{2}k[x - \lambda(t)]^{2}$, with trap strength $k$ and control parameter $\lambda(t)$ the time-dependent potential minimum (fig. 1). To saturate the excess work bounds in (11), (13), we restrict our attention to protocol ensembles where the average protocol $\langle \lambda \rangle_{\Omega}$ is the minimum-work protocol [19]. The SM, sect. III, provides simulation details for each ensemble.

For one control parameter, the theoretical minimum excess work for an ensemble $\Omega$ of driving protocols operating within the linear-response regime (11) with a constant
control parameter velocity variance simplifies to
\[
\langle W_{ex}\rangle_{\Omega} \geq \frac{\mathcal{L}((\lambda)_{\Omega})^2}{\tau} + \langle \zeta(\lambda) \rangle_{\Omega} \langle \delta \lambda^2 \rangle_{\Omega} \tau. \tag{15}
\]

Periodic-potential ensemble. Here the harmonic trap is driven over an underlying periodic potential \( U_{\text{period}}(x) = -\frac{1}{2}E^t \cos \pi x \) with energy barrier \( E^t \) between adjacent wells (fig. 1(d)). Similar potentials have been used to investigate systems with a sequence of metastable states, which are popular models of the basic physics of molecular machines [37]. The generalized friction \( \zeta(\lambda) \) can be expressed as [21,38]
\[
\zeta(\lambda) = \frac{1}{\beta D} \int_{-\infty}^{\infty} \frac{\Pi_{eq}(x|\lambda)^2}{\pi(x|\lambda)} dx,
\]
for equilibrium cumulative distribution function \( \Pi_{eq}(x|\lambda) \equiv \int_{-\infty}^{x} \pi(x'|\lambda) dx' \) and system diffusion coefficient \( D \).

We examine a protocol ensemble where each protocol \( \Lambda \) completes the minimum-work path with an average velocity \( \langle \dot{\lambda} \rangle_{\Lambda} \) randomly sampled from a Gaussian distribution with mean \( \langle \lambda \rangle_{\Omega} \) and variance \( \langle \delta \lambda^2 \rangle_{\Omega} \). Each protocol has instantaneous velocity \( \dot{\lambda} \propto \zeta(\lambda)^{-1/2} \) with the proportionality fixed by the prescribed average velocity \( \langle \dot{\lambda} \rangle_{\Lambda} \). The ensemble-mean control parameter velocity \( \langle \dot{\lambda} \rangle_{\Omega} = \langle \Delta \lambda \rangle_{\Omega} / \tau \) is chosen so that the average protocol \( \langle \dot{\lambda} \rangle_{\Omega} \) completes the control parameter change \( \langle \Delta \lambda \rangle_{\Omega} \) in a prescribed time \( \tau \). The system is initialized in the periodic steady state for a harmonic trap traversing the periodic minimum-work protocol at the particular chosen average velocity.

In the zero-barrier limit, the friction is constant, so the minimum-work protocol proceeds with a constant velocity,
for the harmonic trap moving with the (constant) average velocity of the protocol ensemble.

The control parameter dynamics obey an under-damped Langevin equation (S34) with potential energy $U_\lambda(\lambda, \lambda_0(t)) = \frac{1}{2} k_\lambda [\lambda - \lambda_0(t)]^2$ that is harmonic with spring constant $k_\lambda$ confining the control parameter and time-dependent minimum $\lambda_0(t)$. $\lambda_0(t)$ moves with constant velocity, and throughout the protocol the distribution of control parameter positions and velocities is stationary in the frame which is comoving with $\lambda_0(t)$. As a result, the average control parameter velocity is constant, and the average protocol $\langle \Lambda \rangle_\Omega$ is the minimum-work protocol [19]. The steady-state variance of the control parameter velocity is fixed in the comoving frame by the equipartition theorem, $\langle \delta \dot{\lambda}^2 \rangle_\Omega = \langle \delta \lambda \dot{\lambda} \rangle_\Omega^{-1}$, where $m_\lambda$ is the mass of the control parameter [39]. If control parameter velocity fluctuations persist over time scales longer than the system relaxation time, then (3) holds for all stochastic protocols in the ensemble. Effectively, this represents a locally deterministic limit, where over relaxation time scales of the system, the control parameter is largely unaffected by stochastic fluctuations, but still exhibits large fluctuations over longer time scales (see SM, sect. V, for details).

Figure 3 shows the average excess work as a function of the average protocol duration $\langle \tau \rangle_\Omega$, for several protocol distances $\Delta \lambda$ and control parameter diffusion coefficients $D_\lambda$. Numerical simulations agree well with the theoretical predictions at short protocol durations where the excess work is dominated by the contribution from the average protocol (15). At long protocol durations, for intermediate to large protocol distances and high $D_\lambda$, the locally deterministic approximation (3) is satisfied and the theoretical predictions agree well with the numerical results. In all cases, the excess work is an increasing function of protocol duration in the long-duration limit. Thus, regardless of the theoretical approximation’s accuracy, a finite-time lower bound on the excess work is widely observed, contrary to the case of deterministic protocols.

Discussion. – In this letter, we present a formalism that generalizes previous theory to now quantify the nonequilibrium costs of driving a system with an ensemble of protocols. We assume only that the linear-response approximation applies for each protocol in the ensemble and that variation about the average protocol is sufficiently small. In these limits, protocol variation produces an additional energetic cost that increases with protocol duration.

This theoretical framework gives rise to a lower bound on the excess work (13) that generalizes a previous result [36] to arbitrary low-noise protocol ensembles and situations where the relaxation time varies across control parameter space. Our expression for excess work makes transparent that the lower bound occurs for a finite protocol duration (12) and hence finite average protocol velocity (14a). This implies an energetically optimal, finite time scale for the process, suggesting the novel possibility that biomolecular processes have energetically preferential time scales over which to operate, stemming from the statistical properties of their driving processes.

The resulting total work is completely specified by the average protocol and the variance of control parameter velocities (11), so it may be identical for vastly different control strategies, each with potential advantages for particular tasks. This suggests that an autonomous system could simultaneously reduce the energetic cost of completing a particular thermodynamic process and improve an orthogonal quality metric through the clever choice of the statistical properties of the protocol ensemble (SM, sect. VI).

We have numerically investigated the consequences of these predictions in two model ensembles. Both the periodic-potential ensemble and the stochastic protocol ensemble show a finite-duration minimum for the excess work across all examined parameter space. Complementary recent experiments [40] have shown that, even far from equilibrium, the linear-response formalism can be effective for reducing excess work in control protocols that unfold and refold a DNA hairpin. Thus, the qualitative trends predicted from our theoretical and numerical investigation may still prove insightful for the operational principles of biomolecular machines, even if such machines’ natural operation quantitatively violates linear-response theory.

This theory is agnostic about the origin of such stochastic control parameter fluctuations, assigning work to any energy flow during control parameter changes. Intriguing recent work [41] sheds light on the manner in which nonequilibrium reservoirs can perform work on thermodynamic systems and points toward more biophysically motivated models in which this theory could be applied. Recent research on strongly coupled systems [42] suggests...
connections with the framework developed here, so an open question for future work is the relation of our theory to a broader picture of multiple interacting stochastic systems [43].

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