

When a Bath Is Not Enough: State-Dependent Energy Injection and Nonmonotonic Dissipation in Cytoskeletal Matter

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Living matter consumes energy to build and actuate dynamic protein machines, but the way energy enters these systems is often assumed to be externally imposed and independent of state. This review advances a unifying perspective, that across diverse cytoskeletal active matter, energy injection itself is state dependent, regulated by the mechanical and organizational configuration of the system, rather than acting as a fixed external bath. We synthesize recent experimental evidence, from excitable cortical waves *in vivo* to reconstituted actomyosin networks *in vitro*, showing that feedback between system state and energy input leads to nonmonotonic dissipation, selective energy routing, and relaxation-driven contractility. By organizing these findings within a common framework, we highlight how state-dependent energy injection challenges classical nonequilibrium assumptions and opens new questions for the design and control of active matter.

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I. INTRODUCTION

A. When more fuel does not mean more work

In equilibrium systems, energy is exchanged with the environment via heat or work in a quasistatic, reversible process [1]. In this case, doing more mechanical work (W) typically means spending more energy (U). The conversion of input energy into work is limited by the dissipation of energy (Q). These properties are related by the first law of thermodynamics:

$$\Delta U = Q - W. \quad (1)$$

The more efficient a system is, the more work it can do per unit of energy input. Therefore, more energy dissipation (heat loss) is generally seen as less efficient and less work-producing. More work should require more efficient energy use and less dissipation per unit of work, not more. In this framework, dissipation is viewed as a limitation, an unavoidable “cost” that constrains the efficiency of work [2,3]. By contrast, in nonequilibrium thermodynamics of driven systems, dissipation is not only a cost, but essential [4]. Energy must be injected into the system (via heat or work), and likewise dissipated for work, in a different manifestation, to be extracted [5–7]. In the driven, nonequilibrium case, the system does more work by dissipating more energy [4,8,9]. This gives living systems the appearance of “wasting” more energy as they do more work, which may seem paradoxical. If more and more energy is required to extract work, how do cells achieve precise, coordinated mechanical behaviors without consuming excess energy? Presumably there are mechanisms

to suppress unproductive fluctuations, concentrating the dissipation across certain degrees of freedom, and improving the amount of work per unit of dissipation (a qualitatively different goal than just minimizing dissipation) [10–12]. In general, how does the system redirect energy flow away from futile or disordered trajectories, towards those that are well aligned to do work? Addressing this question involves delineating whether the response occurs in the near-equilibrium or the far-from-equilibrium regime.

B. The limits of linear response

Near thermodynamic equilibrium, the relationship between thermodynamic forces (F_i) and fluxes (J_i) is governed by reciprocity and proportionality [13,14]. In this case, a small perturbation produces a correspondingly small response, and the entropy production rate, Eq. (2) ($\dot{S}$) increases monotonically with the applied drive.

$$\dot{S} = \sum_i J_i F_i. \quad (2)$$

However, each current J_i also grows with its conjugate force F_i [Eq. (3)]. This framework underlies Onsager’s formulation of linear response, in which transport coefficients (e.g., $L_{ij} = L_{ji}$) are symmetric and independent of the strength of the driving [6,7]:

$$J_j = \sum_i L_{ij} F_i. \quad (3)$$

For small $F_i \sim \Delta\mu$, $\dot{S} \propto \Delta\mu^2$. In this case, the chemical potential applied is constant, reflective of chemical energy as a bath. However, the operation of molecular motors and cytoskeletal filaments can lie well outside this regime [4]. Their dynamics couple discrete chemical transitions to mechanical motion through strongly nonlinear rate laws, internal gating, and mechanochemical feedback [15–22] [Figs. 1(a)–1(f)]. As

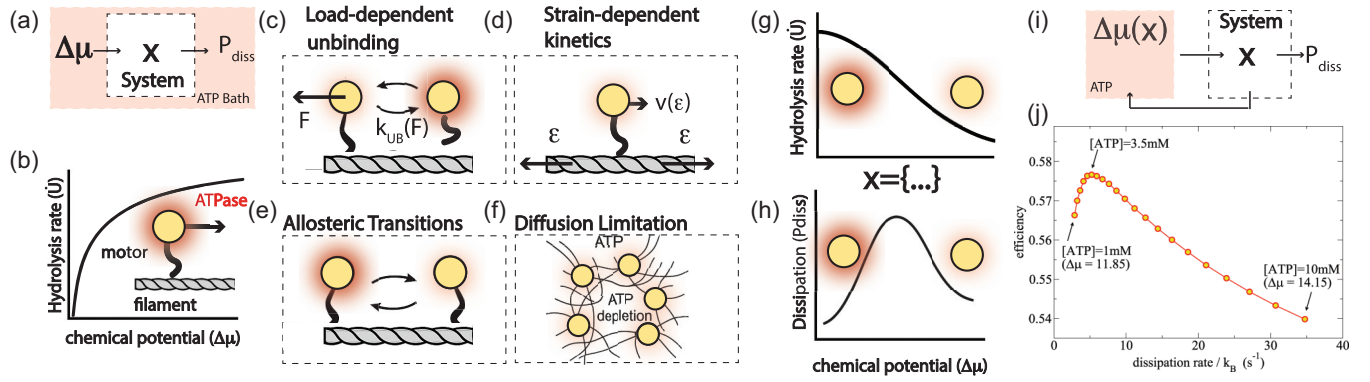


FIG. 1. Constant vs state-dependent energy injection. (a) An open system in which energy injection ($\Delta\mu$) is independent of system internal state, X . ATP is supplied from a bath, which when hydrolyzed by motors leads to (b) a monotonic increase in the internal energy (U). However, there can be nonlinear effects, such as (c) load-dependent binding kinetics, (force, F), (d) impacts from the mechanics of the substrate (strain, ε and velocity, v), (e) changes in motor configurations, or (f) mesoscopic-level effects such as diffusion limitations. (g) The hydrolysis rate can decrease with the nonlinear effects, leading to (h) nonmonotonic dissipation rate, P_{diss} , and potentially energetic efficiency. (i) As the internal state (b)–(e) (and others) can impact the injection of energy, it becomes state dependent. (j) Efficiency of kinesin motors carrying cargo, as determined by a putatively increasing dissipation rate [23].

the chemical potential difference driving ATP hydrolysis increases, these couplings can reorganize so that additional fuel no longer translates into proportional work or heat. To this end, far from thermodynamic equilibrium, the same energetic input (ATP availability) can produce different outputs depending on the kinetic, structural, or mechanical state of the system.

The two-state model of kinesin developed by Lau, Lacoste, and Mallick [24] captures the departure from linear response by exploring the two-way relationship between chemical energy consumption and mechanical work performed by molecular motors. In this work, Onsager reciprocity (between chemical and mechanical subsystems) is violated because ATP hydrolysis drives the system around a nonequilibrium chemical-mechanical cycle, breaking detailed balance and producing asymmetric cross-coupled response coefficients [24]. As a result of this violation, chemical driving ($\Delta\mu$) can naturally produce a nonmonotonic energetic efficiency (and dissipation) [Figs. 1(g)–1(j)]. At high $\Delta\mu$, mechanochemical coupling breaks down, and futile cycles proliferate. While this work describes mechanical load dependence as a mechanism for the decoupling of fluxes, there are a variety of ways in which motors may alter their consumption of chemical energy, performance of work, or both. Internal strain gating and allosteric conformational coupling can delay ATP binding [25] or alter catalytic step energetics [26,27], while the filament's nucleotide state [28] and the local ionic or pH environment modify P_i release and actomyosin affinity [29,30]. At larger scales, network ensemble elasticity [31,32], crowding and diffusion limits [33,34], regulatory feedback [35], and cytoskeletal connectivity can all slow turnover [36], shift motors between activity states, or impede depolymerization, thereby reshaping effective ATP consumption. Separately, Baiesi and Maes suggest that nonmonotonic behavior (e.g., efficiency) emerges naturally from not only dissipation, which arises from time-antisymmetric behaviors, but time-symmetric kinetic processes (frenesy) that dominate far from equilibrium [23]. In either case, these findings sug-

gest that once mechanochemical coupling becomes strong, additional driving can restructure rather than amplify dissipation, revealing a feature of active systems that operate far beyond the limits of linear response.

C. When ATP stops being a bath

While it is well understood that complex, overlapping feedback loops exist between biochemical regulatory elements, such as gene expression networks or protein-protein interactions, this type of feedback occurs between internal variables within the system. Indeed, most active gel and active nematic theories already include state-dependent stresses, nonlinear feedbacks, and cross-coupled Onsager coefficients. In those frameworks, however, the chemical driving force (e.g., ATP or $\Delta\mu$) is still treated as fixed by a reservoir. The energy source acts as a bath, while only the response depends on state. It remains less clear, however, whether such feedback extends to a deeper thermodynamic level: Does the mechanical or organizational state of the system influence the *injection* of energy itself? If so, this suggests that chemical energy, such as ATP, no longer serves as a bath, in which it is a fixed chemical potential. Instead, the ATP may be a dynamically coupled subsystem with finite degrees of freedom. Indeed, evidence suggests that ATP concentration is not spatially uniform, as it varies across organelles [37,38], fluctuates spontaneously [39], is reaction-diffusion limited near where utilized [33], varies with cell maturation stage [40], is responsive to mechanical stress [41] and activity [42,43], and can be depleted by cytoskeletal activity [44,45]. Without uniformity, constancy, and independence of system dynamics, reciprocity and linear response may not apply, and dissipation need not be monotonic. Thus, we need to move beyond stochastic thermodynamics of fixed baths and models with constant activity parameters, into a new territory on the thermodynamics of interacting driven subsystems.

This review considers that active or living systems are distinguished from traditional physical systems not only by their

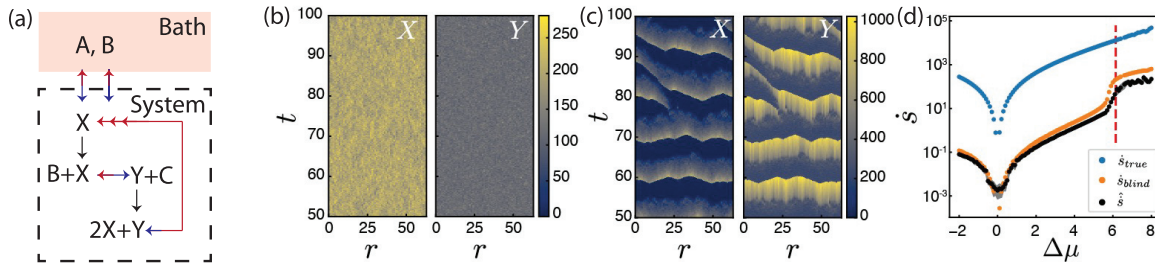
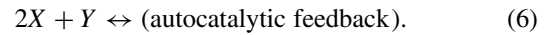
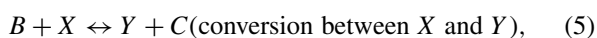
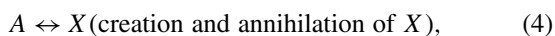


FIG. 2. Entropy production rate is monotonic with chemical potential in the Brusselator. (a) Inputs to the Brusselator are reflective of a constant chemical potential, which acts as a bath. Chemical species X and Y , (b) with no chemical potential, which does not yield oscillations, and (c) with high chemical potential with oscillations. (d) The increase in the chemical potential increases the entropy production rate, to drive the system from uncorrelated oscillations to correlated oscillations. The system passes through a Hopf bifurcation at the dotted red line. Taken from Ref. [58].

consumption of energy, but that energy is injected depends on the system's own state. Rather than treating the driving force as fixed and external, as in standard nonequilibrium thermodynamics, experiments now show that the cytoskeleton, as a model active material, feeds back on its own energy supply through mechanosensitive enzymes, load-dependent motor activity, and stress-regulated remodeling. This perspective allows us to reconcile a range of seemingly paradoxical results, such as nonmonotonic entropy production and efficiency, the diversity of molecular mechanisms for dissipating energy, and the energetic costliness of dynamically stable, noncontractile states, and to connect them into a coherent picture. Thus, our aim is not to introduce new data or models, but to synthesize *experimental* findings, based on recent results on actomyosin as a quintessential active-matter system, into a conceptual framework that highlights how energy input is modulated by internal state.

In the following sections, we review how systems with constant energy injection (i.e., energy is a bath) behave distinctly from those whose energy injection depends on their internal compositional, mechanical, or organizational state of the system (i.e., energy is a subsystem). Then, we discuss the consequences of state-dependent energy injection, including violation of linear response, broken reciprocity and the reallocation or “rerouting” of energy among subsystems, and the selection of diverse molecular mechanisms (pathways) by which energy is dissipated. We then review how these pathways translate to mesoscale dissipation within the framework of self-organized criticality. Finally, we discuss the implications of a state-dependent injection framework for the physics of living systems.

Part 1: When energy injection determines system state. Reaction-diffusion systems maintain spatial patterns or oscillations in local chemical concentrations (e.g., X & Y), fueled by nonzero chemical potentials ($\Delta\mu$, e.g., substrate supply). X & Y are created, annihilated, and converted through nonlinear feedbacks, which can lead to spatial and temporal patterns. An example of dynamical instabilities in a reaction-diffusion system is the reversible Brusselator, a model for an autocatalytic chemical reaction [46–50] (see Fig. 2):



Each reaction has forward and backward rates: $k_1^{+/-}$, $k_2^{+/-}$, and $k_3^{+/-}$, respectively. A , B , and C act as constant reservoirs and sinks, maintaining nonequilibrium conditions [Fig. 2(a)]. In the model, the conversion of different chemical species is driven by a chemical potential:

$$\Delta\mu = \log \frac{Bk_2^+k_3^+}{Ck_1^-k_3^-}. \quad (7)$$

When $\Delta\mu = 0$, detailed balance holds, and the system is at thermodynamic equilibrium [Fig. 2(b)]. When $\Delta\mu \neq 0$, detailed balance is broken, and the system is out of equilibrium [Fig. 2(c)]. Thus, the state variables (x , y) determine how the concentrations evolve over time, but they do not influence the driving force itself. In other words, $\Delta\mu$ is fixed by the reservoirs and acts as an input knob that is independent of the system's internal state.

When detailed balance is broken, there are net fluxes of energy [51,52]. Thus, by quantifying the irreversibility of the system dynamics, one can estimate the production of entropy $\dot{S}$, a correlate to the dissipation of energy [51]. The entropy production rate (EPR, $\dot{S}$) is defined using the Kullback-Leibler (KL) divergence between forward and time-reverse trajectories [10,53–55]:

$$\dot{S} = \lim_{T \rightarrow \infty} \frac{1}{T} D_{\text{KL}}(P[X] || P[\tilde{X}]). \quad (8)$$

Here, $X(t)$ is a trajectory of system variables over time, and $\tilde{X}$ is the time-reversed trajectory. $P[X]$ and $P[\tilde{X}]$ are their respective probabilities. The function D_{KL} is the Kullback-Leibler divergence ([56]), which measures how distinguishable two probability distributions are by capturing the degree of irreversibility in the dynamics.

(i) For no driving ($\Delta\mu = 0$), the system is at equilibrium, and well mixed (no waves), and no entropy is produced ($\dot{S} = 0$) [Figs. 2(b) and 2(d)].

(ii) For weak driving, as the chemical potential is increased ($\Delta\mu > 0$), the system undergoes oscillations in the concentrations of chemical species (waves). At the onset of oscillations, there is a large jump in $\dot{S}$ [57] [Figs. 2(c) and 2(d)].

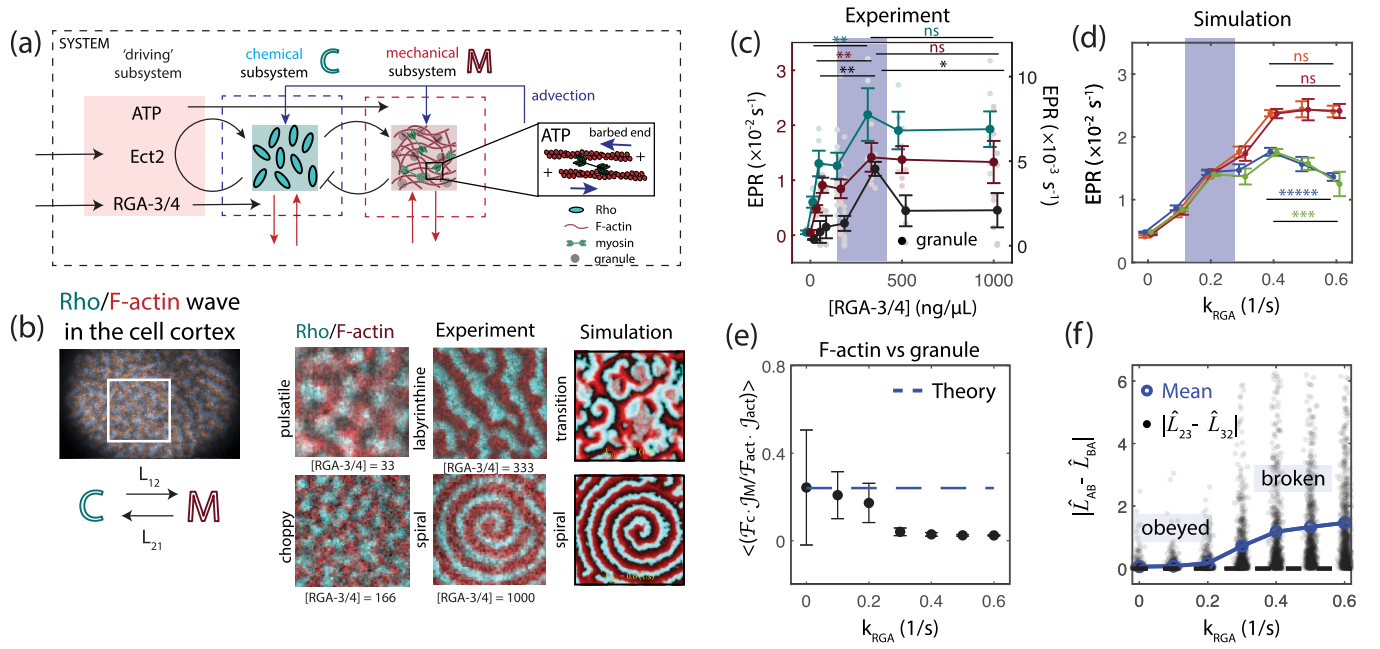


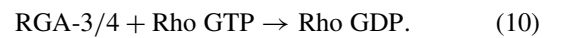
FIG. 3. Entropy production rate is nonmonotonic with driving in the excitable cytoskeleton. (a) In *Xenopus* oocytes, chemical subsystems (Rho interacting with actin), and mechanical subsystems (actomyosin generating contractility as visible by the motion of pigment granule) interact through activation Rho agonists and antagonists. Driving forces (pink box) can no longer be considered a bath, as internal variables and feedbacks will determine their utilization. The mechanical subsystem is driven by the chemical subsystem through F-actin polymerization, and the chemical subsystem is driven by the mechanical subsystem through contractility which flows and concentrates Rho (“advection”). (b) Image of the oocyte, with Rho (blue) and actin (red) highlighted. Schematic describes Onsager reciprocity, with chemical subsystem (C) driving mechanical subsystem (M) and vice versa (L_{12} and L_{21} , respectively). The system is reciprocal if C influences M to the same extent that M influences C ($L_{12} \sim L_{21}$). [(b), right] Exogenous Rho GTPase activating (RGA) protein variation results in different dynamical phenotypes that are reproduced by reaction-diffusion models coupled to viscoelastic materials. (c) RGA (experiment) and (d) k_{RGA} (model). (e) Ratio of Onsager’s entropy produced by mechanical dynamics, to F-actin dynamics and (f) difference in Onsager coefficients (actin/granule). The purple bars reflect the range of temporal wave frequencies in the RGA-manipulated oocyte that resemble the natural, nonexogenously manipulated early developmental stage oocyte prior to cell division (“natural state”). Taken from Ref. [62].

(iii) For strong driving, although with only a small further increase in $\dot{S}$ ($\Delta\mu \gg 0$), the system transitions from disorganized (random-in-time) oscillations to synchronized (periodic-in-time) oscillations, where oscillations coordinate their periodic behaviors through internal coupling mechanisms (4)–(6). Thus, one can consider the cost “expensive” to establish waves, but comparatively cheaper to synchronize them.

The system injection of energy is fixed (constant), and there is a monotonic relationship between $\Delta\mu$ and $\dot{S}$. Thus, in the Brusselator, the form of the protocol is the following: input $\rightarrow$ response [Fig. 1(a)].

Part 2: When system state determines energy injection. Excitability refers to the ability of the cortical cytoskeleton, which is a thin, contractile layer of actomyosin beneath the plasma membrane, to undergo Brusselator-like transient, self-organized pulses or waves of contraction in response to internal or external stimuli [35,58–61] and plays critical roles in cell polarization, migration, division, and morphogenetic events [58] [Figs. 3(a)–3(d)]. Actomyosin is a composite of filamentous protein (F-actin), which assembles and disassembles, and myosin II molecular motors, which bind, and impart mechanical stresses [63]. Both processes require the hydrolysis of ATP, which provides the underlying chemical potential, but are driven upstream by diverse chemical species.

In the *Xenopus* oocyte, the combined expression of Ect2 and RGA-3/4 converts the cortex into an excitable medium [61] [Figs. 3(c) and 3(d)]. Ect2 converts Rho GDP (inactive) to Rho GTP (active) via positive feedback from active Rho [35,61]. RGA-3/4 converts Rho GTP to Rho GDP via negative feedback from Rho and F-actin [64]. By this analogy, $X \sim$ active RhoA (excitable trigger, autocatalytic), and $Y \sim$ F-actin or actin-associated inhibitor (delayed negative feedback):



Thus, biochemical regulators drive mechanical behaviors, such as F-actin assembly and contractility (i.e., chemical force drives mechanical flows, L_{12}). At the same time, actin cortex contraction may condense Rho embedded within it, thereby altering its chemical activity (i.e., mechanical force drives chemical flows, L_{21}). Together, these feedbacks provide a mechanism by which cells can localize contractile activity through dynamic thresholds rather than sustained input, driving the system through diverse patterns of Rho, membrane-embedded granule, and actin. By cross-correlating the Rho and actin image time courses, one can estimate the EPR for the “chemical subsystem” ($\dot{S}_{\text{chem}}$) and by correlating

TABLE I. Internal variables in actomyosin networks.

Variable (X)	Captures	Contractile (low $\dot{S}$)	Stable (high $\dot{S}$)
Nematic order, m	Geometric alignment	High	Low
Bundling, q	Structural change	High	Low
Velocity alignment, v	Coherent motion	High	Low
Fluctuation anisotropy, φ	Axial or transverse noise	axial	Transverse
Phase-space circulation, ϕ	Time symmetry	Modest coherence	Disordered
Net filament polarity, p	Configurational change	High	Low
Fluorescence intensity, I	Material density	Variable	Constant
Mechanical stress, σ	Force per unit area	High (low cycling rate)	Low (high cycling rate)
Mechanical strain, ε	Material deformation	High	Low

the actin and granule microscopy image time courses, the EPR for the “mechanical subsystem” ($\dot{S}_{\text{mech}}$). Thus, one can assess how $\dot{S}$ changes with driving (RGA-3/4), but by comparing the EPR to Onsager coefficients (L_{12} - L_{12}), one can estimate the “energetic costs” of reciprocity [Figs. 3(e) and 3(f)]:

(i) For $\Delta[\text{RGA-3/4}] = 0$, the system is quiescent and there are no oscillations.

(ii) At low $\Delta[\text{RGA-3/4}]$, the system begins to pulse similarly in Rho, actin, and granule [Figs. 3(b)–3(d)], suggesting a coupling between chemistry and mechanics. However, the pulses are not coherent, reminiscent of the low entropy oscillations in the Brusselator. Pulses have low $\dot{S}_{\text{chem}}$, and $\dot{S}_{\text{mech}}$ and reciprocity is maintained ($L_{12} \sim L_{21}$) [Figs. 3(c)–3(f)]. It is suggested that L_{21} arises from actomyosin contractility, which induces flow and condensation of the chemical species, thereby altering their dynamics.

(iii) For increasing $\Delta[\text{RGA-3/4}]$, there are “choppy” and then labyrinthine and then spiral waves. Choppy waves have modest $\dot{S}_{\text{chem}}$, and $\dot{S}_{\text{mech}}$ and $L_{12} \sim L_{12}$. Labyrinthine waves have the highest $\dot{S}_{\text{chem}}$ and $\dot{S}_{\text{mech}}$, and L_{12} and L_{12} begin to diverge. However, for spiral waves, $\dot{S}_{\text{chem}}$ remains high, and $\dot{S}_{\text{mech}}$ is decreased, and reciprocity is broken ($L_{12} \neq L_{12}$), due to a mismatch in chemical and mechanical timescales (e.g., relaxation) due to the enhanced driving.

Thus, unlike the Brusselator, $\dot{S}_{\text{mech}}$ is nonmonotonic with driving (RGA-3/4) [Figs. 3(c) and 3(d)], and the peak in $\dot{S}_{\text{mech}}$ occurs at the last point at which the system remains reciprocal. This finding suggests that, at low driving, energy is proportionally allocated between chemical and mechanical subsystems. However, at high driving, they are uncoupled, and energy is disproportionately allocated. Thus, nonmonotonicity in this case, implies that at some point, dissipation is not amplified, but restructured or rerouted. Thus, the two cases have similar “energetic cost” (low and high driving may have the same $\dot{S}$), but the energy is allocated differently.

Interestingly, the Rho-actin dynamics that characterize the wave frequencies that precede cytokinetic ring assembly in the early stages of maturation, prior to cell division (natural, nonexogenously manipulated cortex), lie proximal to the peak in $\dot{S}_{\text{mech}}$, suggesting that the cell cytoskeleton is not only poised at a dynamical phase transition (e.g., Hopf bifurcation, as has been suggested previously [35,64–66]) but also one marked by energetic signatures. Furthermore, these signatures arise from both chemical and mechanical feedbacks that regulate the diverse chemical potentials that drive the system.

Thus, in this case, the form of the protocol is the following: input $\rightarrow$ response $\rightarrow$ input [Fig. 1(i)].

However, it should be noted that $\dot{S}_{\text{mech}}$ is reflective of subsystem dynamics, not the entire system, nor its partner subsystem. Second, RGA-3/4 is not the true chemical potential, as it may not directly reflect a nucleotide state (which is unknown). Yet, we ask a general question: When does monotonicity break down? Do different molecular mechanisms (e.g., actomyosin interactions) uniquely characterize the states with different energy allocations? In a living system like the oocyte, there are many unaccounted-for components and interactions, which may make differentiating mechanisms of nonmonotonicity difficult. Instead, one desires a complete thermodynamic system, in which protein and nucleotide composition can be controlled precisely, and energy fluxes measured. Next, we describe interactions within the cytoskeleton that may relate to nonmonotonicity.

Observation 1: Actomyosin interactions depend upon system stress and strain. Reconstituted systems, composed of purified protein, reproduce diverse dynamics and mechanics of the actin cytoskeleton [34,67–94]. For any protein or nucleotide composition, we can define the state of the system by X (Table I). Within X , the density of myosin filaments (ρ) determines the active stress (σ) and the dynamical state of the system ($x(t)$, $y(t)$) (Fig. 4). At constant ATP concentration, and below some critical density (ρ_c), the network does not fully contract, but actin filaments experience reversible bending fluctuations about some small, mean strain [Figs. 4(b)–4(f)]. By contrast, for the same nucleotide conditions and ρ above ρ_c , the network condenses completely, achieving a high strain. The former is a “stable” steady state (S_1) as the strain has achieved a constant value (no flow), and the later state is a “contractile” state (C) at constant strain rate (flow). Assuming both S_1 and C to be steady states (over some experimental time frame), one can correlate different bending modes, yielding a phase space flux, ϕ , and an entropy production, $\dot{S}$ [51,52] [Fig. 5(a)]. If bending modes are uncorrelated, there is no flux ($\phi = 0$, $\dot{S} = 0$). By contrast, when they are correlated, there is a measurable circulation ($\phi \neq 0$, $\dot{S} > 0$). It was shown that bending fluctuations yield a stronger circulatory flux when stable than contractile [$\phi_S > \phi_C$ Figs. 5(b)–5(f)]. Thus, in a subset of the overall activity of the system, $\dot{S}$ is greater in the stable case than the contractile case, yielding a nonmonotonic dependence of $\dot{S}$ on ρ [Figs. 5(c)–5(e) and 6]. Again, in this case, the driving (ρ) is not necessarily the chemical potential (ATP), but a correlate [23].

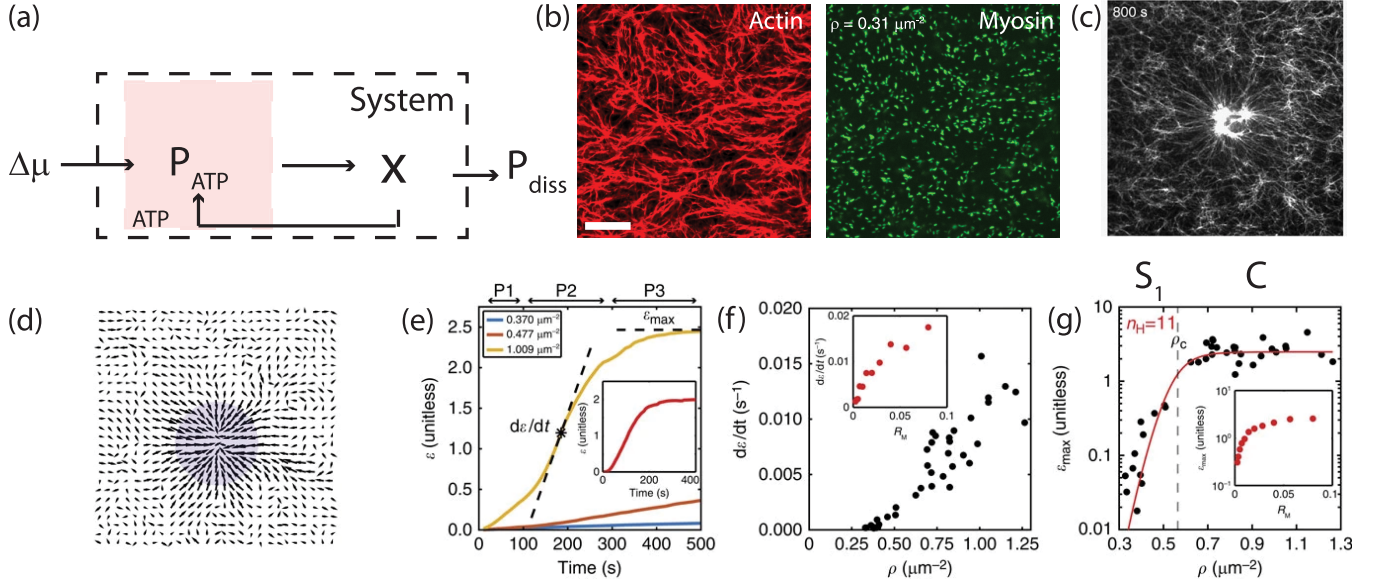


FIG. 4. Driving differentiates dynamically stable states from contractile states. (a) ATP serves as a subsystem, due to the load-dependent behavior of myosin (X), which modulates the rate of ATP hydrolysis (P_{ATP}). (b) Images of an F-actin network (left) and myosin thick filaments at a certain density, ρ . Scale bar is 10 μm . (c) The energy injected into the system can be controlled by using blue light to inactivate Blebbistatin, a myosin ATP inhibitor. (d) The internal dynamics are quantified by particle image velocimetry (PIV), as occurs with inactivation of Blebbistatin within a central region (purple). (e) Measurements of strain (ϵ) and strain rate ($\dot{\epsilon}$) indicate two regimes: a stable system which ceases to condense after some initial strain (S_1), as determined by myosin density, ρ , and a contractile state which evolves to the same strain regardless of myosin filament density (C). Thus, the former is characterized by a constant strain, and the latter a constant strain rate. Insets reflect computational simulations of actomyosin systems with identical control parameters. Taken from Ref. [77].

The transition between S_1 and C can be reproduced for a more complete F-actin network encapsulated within emulsions, where ATP consumption (P_{ATP}) and mechanical work (P_{mech}) are measured directly [Figs. 7(a)–7(c)]. In this case, difficult steady-state assumptions do not need to be made. The transition between stability and flow can be induced at a constant ρ , but by exchanging proteins that influence the organization or dynamics of the actin network itself. For example, F-actin bundling (q) or net polarity (p) is altered

by F-actin cross-linkers and nucleators such as Arp2/3 and formin, which grow branched or linear F-actin, respectively (Fig. 6). The dynamics of F-actin turnover is altered by proteins that impact connectivity or rigidity and fluidity, such as cofilin and gelsolin [95,96]. With either change in configuration (at a constant ρ), the system transitions between S_1 (at high P_{ATP} , low P_{mech}) and C (at low P_{ATP} , high P_{mech}) [81,83] [Figs. 7(d)–7(f)]. Indeed, for most configuration combinations, P_{ATP} and P_{mech} are linearly proportional to each

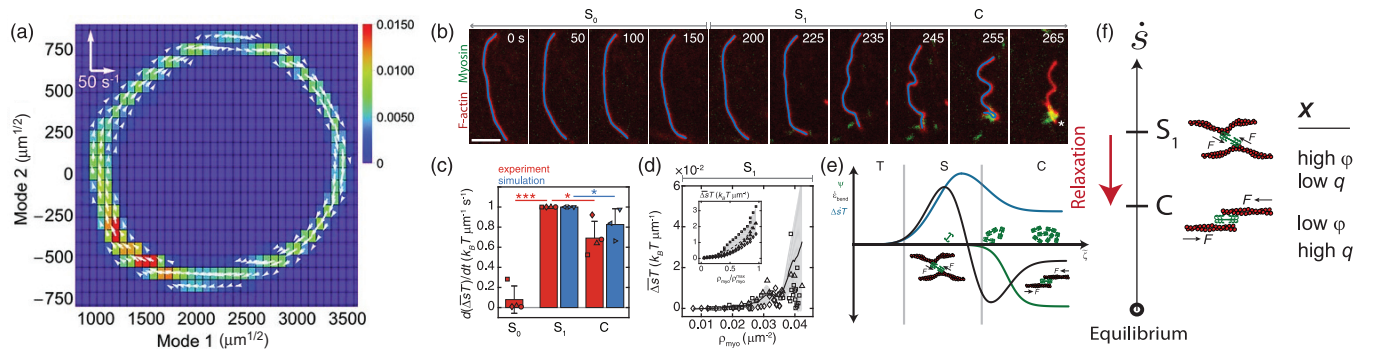


FIG. 5. EPR is nonmonotonic with myosin density and differentiates distinct internal pathways for dissipating energy. (a) Correlating bending fluctuations for a fluctuating axoneme yields a phase space, which demonstrates circulation and broken detailed balance. Taken from Ref. [51]. (b) Bending fluctuations of F-actin in stable states (S_0 , no myosin/thermal; S_1 , active but below ρ_c) and contractile states (C, above ρ_c). S_1 has a constant strain, and C has a constant strain rate. (c) EPR based on bending fluctuations for each state. (d) EPR as a function of myosin density for S_1 . Inset reflects computational simulation with identical control parameters. Taken from Ref. [78]. (e) Diagram of how the EPR and internal variables evolve as a function of driving, from thermal (T), to stable (S) and contractile (C). (f) EPR indicating the stable states are further from thermodynamic equilibrium than contractile states, and the associated state variables that change in this transition (alignment q , fluctuation anisotropy, ϕ). In the stable state, nonproductive “plucking” of actin filaments is the predominant pathway, while in the contractile state, antiparallel sliding is the predominant pathway.

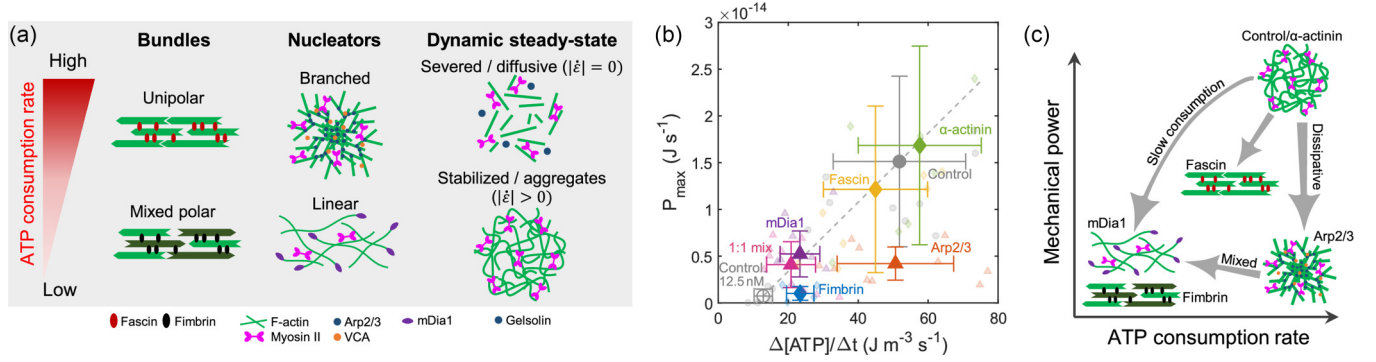


FIG. 6. Mesoscale organizational state determines microscale ATP consumption. (a) Altering F-actin configuration yields different dynamical states. This result includes the extent of bundling (b) by F-actin cross-linkers that yield unipolar or mixed-polar filaments (p), Arp2/3 vs formin, which creates branched or linear networks, and the presence of cofilin or gelsolin that alters filament length and F-actin turnover. (b) Most ATP consumption ($P_{ATP} = \Delta[ATP]/\Delta t$) is proportional to power output ($P_{\max}$, the maximum of P_{mech}), but not always. (c) Diagram representation of F-actin organization on the relationship between power and consumption rate. Taken from Ref. [81].

other, suggesting a potential common principle [Fig. 6(b)]. However, there are exceptions. Notably, in this assay, Arp2/3 performs little work (presumably in the lack of antiparallel filaments to slide) yet dissipates a lot of energy [Figs. 6(b) and 6(c)]. Indeed, previous work has indicated that contractility is abrogated in the presence of highly branched networks [79], in contrast to other studies [72,94,97,98].

Disparate dissipative pathways. Despite a constant ATP concentration for experiments with different ρ , the interactions between actin and myosin vary. For S_1 , there is filament “plucking” in which myosin repeatedly and reversibly binds and motors filaments [78] [Table II, “pathway 1”; Fig. 5(e)]. This behavior yields transverse F-actin bending that is rapid and reversible, and leads to no significant net strain over time [Fig. 5(d)]. In this case, there is significant anisotropy in filament fluctuations, as fluctuations occur principally perpendicular to their long axis. By contrast, in C , myosin slides actin filaments relative to each other, as expected from canonical crossbridge interactions [Table II, “pathway 2”; Fig. 5(f)]. This results in a net condensation, and a flow of the system [Fig. 4(d)]. During this flow (not when condensed), there are fluctuations that are along their long axis, and thus a correla-

tion between the alignment of the actin (φ), and their velocity, which can be representative of an increased “order” in the contractile state compared to the stable state. Furthermore, the relative motion between actin and myosin is negligible, indicating that myosin motion along actin has slowed by the catch-bond nature of the crossbridge [102]. As the sliding accumulates load, and is slow, $\dot{S}$ is lower than in plucking, in which load does not accumulate. Alternatively stated, the stable state is further from thermodynamic equilibrium than the contractile state despite a higher driving force (myosin density) in the contractile state [Figs. 5(b)–5(e)]. Taken together, these results may suggest that the contractile state is a relaxation of energy from the stable state [Figs. 5(f) and 7(f)].

What are the implications of a more energetically expensive stable state? Entropy production can peak at intermediate levels of driving, before a system organizes into coherent work-producing structures. This challenges the common intuition that “more structured = more dissipative” [48,103]. Furthermore, even though macroscopic contraction is irreversible (i.e., once a network shortens and compacts, it does not spontaneously extend), its microscopic pathways may be more organized and symmetric. While contracting, the

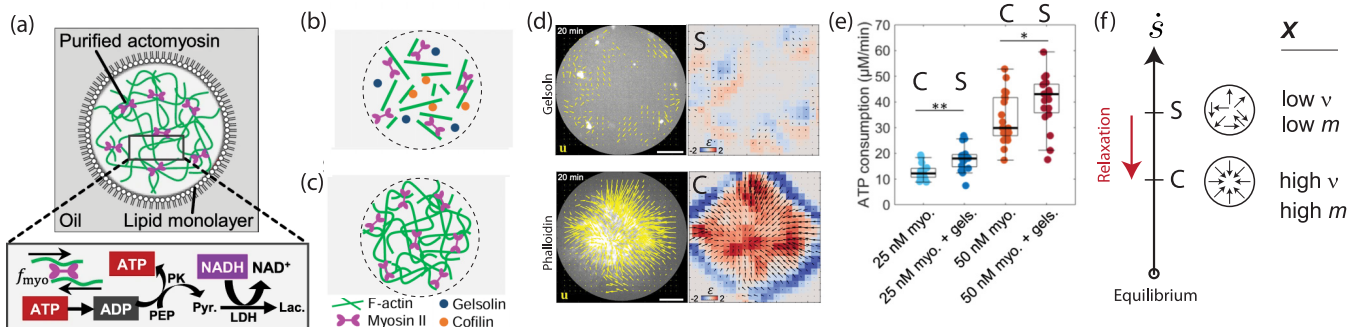


FIG. 7. Energetic costs of stability and contractility via motoring and relaxation. (a) Actomyosin network within emulsions. ATP regeneration system is present. Either the system (b) has a high degree of F-actin turnover, through the activity of gelsolin and cofilin, or (c) is stabilized by phalloidin. (d) Left, F-actin fluorescence; right, vector field, displaying motion of actin (fluorescence); top, with gelsolin; bottom, with phalloidin. Scale bar is 10 μm . (e) ATP consumption rate. Taken from Ref. [81]. (f) Diagram of EPR suggesting that the energy consumed in making the system highly dynamic and relaxing internal stresses is more energetically expensive than one in which there are contractile flows. v is velocity, m is nematic order.

TABLE II. Preferred pathways for dissipation.

Microscopic	Condition	$\dot{W}_{\text{extracted}}$	$\dot{S}$	Macroscopic
0, Myosin walking	Friction/steric	Low	High	Stability (S)
1, Filament “plucking”	Low myosin density	Low	High	Stability (S) [78,99,100]
2, Actomyosin sliding	High load	Medium	Low	Contractility (C), alignment
3, Viscous relaxation	High actin turnover	Low	High	Stability (S) [101]

actin can align in the direction of flow. Thus, there can be high nematic order, m (depending upon the initial condition), and high velocity correlation, v . As a note, irreversibility in nonequilibrium systems must be judged at the scale of the relevant degrees of freedom. Thus, the fact that the network flows irreversibly does not necessarily mean that it is further from thermodynamic equilibrium than the one that goes nowhere. Second, if stability is more energetically expensive (rapid, low-load myosin motions, or ATP-dependent assembly and disassembly), then contractility may be a relaxation of energy from a state with a higher dissipation of energy [Fig. 7(f)].

Observation 2: De novo myosin assembly depends upon the organizational state of actin. Self-organized criticality (SOC) is typically associated with systems poised near a dynamical instability [104–106]. In this case, a dynamical system naturally evolves to a critical state, where it exhibits scale-invariant (power-law) fluctuations without fine-tuning of parameters. For example, mechanical energy can be accumulated slowly, but is dissipated quickly. If the system interacts across many sites within the material, the released stress can trigger cascades, leading to scale-free statistics, the hallmark of SOC (e.g., avalanches). Indeed, recent work has indicated that mechanical stress in the cell cytoskeleton can accumulate slowly but is released quickly and dramatically [107–109] (Fig. 8). The distribution of relaxation events can be power-law distributed, resembling what is found in earthquakes and landslides [87].

As previously mentioned, energy that is accumulated and dissipated within actomyosin will depend upon F-actin organization [98,110–112] as determined by the relative concentration of nucleators such as formins [79,113] or Arp2/3 [114,115] (Fig. 6) [115]. However, only when F-actin is branched to a certain extent does myosin accumulate stress slowly, which then leads to large cascades. This may be due to the myosin-dependent breakage of actin at specific sites in the branched actin network “tree” [116]. The severing of small branches (which are numerous) leads to small dissipative events, while severing of large branches (which are few) leads to larger dissipative events [Figs. 8(c)–8(e)]. However, there is also evidence that the organization of the actin network determines the *ab initio* stress applied [110,111].

Linear networks nucleated by formin entangle into a loose network that facilitates myosin dimer binding, elongation, and contraction [Fig. 8(c)]. By contrast, branched F-actin networks are dense and nonaligned, and thus thick filaments can be “caged,” or geometrically constrained [79,117]. As a result, myosin binds to F-actin, but is unable to exert significant mechanical stresses when disallowed from sliding filaments. Furthermore, F-actin organization can determine the polymerization state (size) of myosin itself, L . Branched networks limit the elongation of thick filaments (potentially also due to steric effects) while linear networks enable their elongation to some maximum length, L_{myo} . As the force generated by thick filaments scales with the number of motors within the filament, the organization of the F-actin determines the assembly

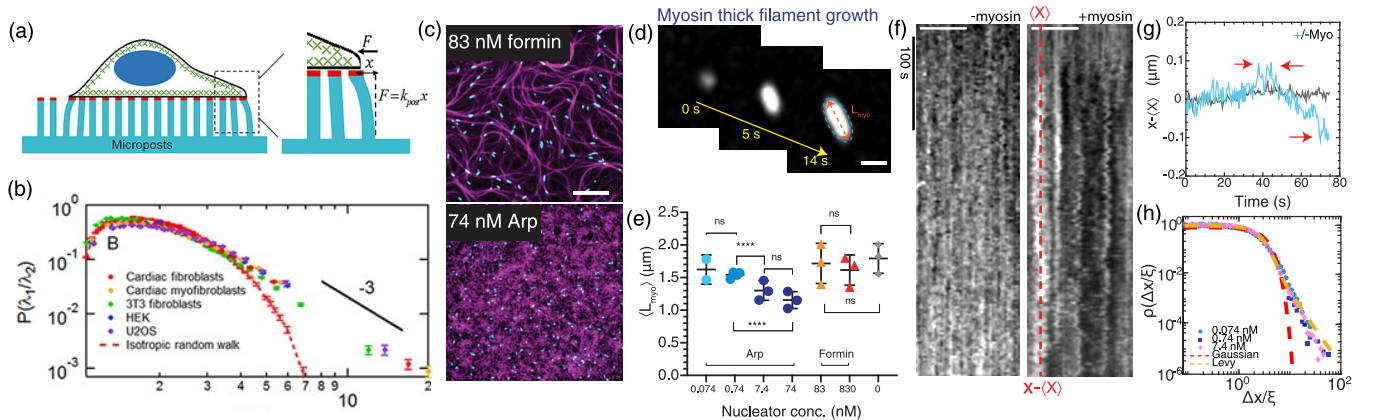


FIG. 8. Self-regulated stress and self-organized criticality. (a) Cells adherent to microposts deform them with force, F . (b) Anisotropy of post fluctuations (λ_1 and λ_2 are the semimajor and semiminor axes). (a) and (b) taken from Ref. [109]. (c) Quasi-2D polymerized actin networks adjacent to a model cell membrane, assembled by different nucleators, decorated with myosin II motors. (d) Growth of myosin II thick filaments from dimers, within an actin network. (e) Mean thick filament lengths as a function of the F-actin nucleator conditions (different organizations). (f) Kymographs in an actomyosin network before and after the addition of myosin. Spatial fluctuations $x - \langle x \rangle$ are about a mean actin position ($\langle x \rangle$). Mean is indicated by dotted red line. (g) Fluctuations in actin over time before and after myosin addition. (h) Probability density function of fluctuations. Levy- α fit reflects avalanchelike behavior.

of the myosin motor filaments [87,118,119] and, in turn, how much energy is injected into the system.

Phenomenological representation of thermodynamic feedback. Across diverse active-matter systems, there is feedback between system variables that regulate system phenomenology and dynamics [120]. For example, in the active gel model, when feedback exists between flow and activity, it fundamentally serves to control the spatial and temporal patterning of stress generation and dissipation [19,114,121–127]. This feedback does not typically modulate how much energy is injected overall, but how that energy is spatially deployed and converted into work. Can we model nonequilibrium systems to include feedback upon thermodynamic variables? Let us define, for an actomyosin system, U as the total microscopic energy in the system. This includes stored mechanical strain energy in the network due to filament tension and cross-link stretching. It also includes chemical energy reservoirs, e.g., ATP molecules bound to myosin or actin. This work (W) can include contractile work performed by the actomyosin system on surroundings (e.g., extracellular matrix (ECM), substrate) [128–130]. The heat (Q) includes ATP hydrolysis, conformational changes of protein, and frictional losses. The change in W or Q over time is referred to as a power and dissipation rate, which we use the variable P for both:

$$\frac{dU}{dt} = P_{\text{ATP}} - P_{\text{mech}} - P_{\text{diss}}. \quad (11)$$

In this equation, P_{ATP} is again the injection rate of energy into the system, P_{mech} is the mechanical work output per unit time (power), and P_{diss} is the rate of energy dissipation. We therefore propose a phenomenological description in which the chemical input $\Delta\mu$ is not fixed by an external reservoir, but regulated by the system state itself, X :

$$P_{\text{ATP}} = \zeta[X] \cdot \Delta\mu, \quad (12)$$

where ζ modifies the impact of a basal $\Delta\mu$ (e.g., unloaded ATP hydrolysis by myosin motors). This differs from conventional active gel models, where activity enters as a prescribed constant (or externally controlled parameter) multiplying stress or flux terms. Here, instead, the magnitude of energy injection becomes a dynamical variable, coupled to stress, structure, or organization.

In this review, we synthesize growing experimental evidence indicating that the compositional, mechanical, and organizational states of the system regulate the injection of energy (P_{ATP}) such as stress (σ) [131–134], bundling (b), polarity (p), or geometric parameters, such as the effects of confinement on L . These constraints will determine the dissipative pathway (e.g., plucking vs sliding; see Table II), and the overall dissipation rate P_{diss} .

II. DISCUSSION

Across a broad range of driven soft-matter systems, feedback between internal variables, such as the coupling of activity, order, and defect motion in active nematics described by Yeomans [135–137] and Gardel [34,138], or the competition between binding and rearrangement pathways in Hagan’s analyses of self-assembly [139,140], produces characteristic nonlinear and sometimes nonmonotonic system *dynamics*.

These mechanisms highlight how dissipation and structure coevolve, but they treat the energy input as fixed and independent of the system’s state. In this review, we have demonstrated that the compositional, mechanical, and organizational states of the system regulate the injection of energy into the system, and therefore the energy source is no longer independent (e.g., a bath), but conditional (e.g., a subsystem).

Recent calorimetric measurements of active cytoskeletal materials further underscore the importance of distinguishing energy injection from macroscopic motion. In microtubule-based active gels, only approximately 10^{-9} of the total dissipated power propagates to the scale of emergent flows, demonstrating a dramatic scale-dependent decoupling between microscopic energy consumption and macroscopic structure [141]. Such results reinforce that dissipation measured at one scale need not directly track organization at another. If energy injection is conditional and internally regulated, then the relationship between microscopic consumption and macroscopic motion need not be straightforward.

Can such a process be thermodynamically consistent? Both equilibrium and nonequilibrium processes are governed by the first law of thermodynamics, which states that the change in a system’s internal energy equals the net energy transferred as heat and work [Eq. (1)]. Whether the process is a reversible, quasistatic transformation or an irreversible, path-dependent one, energy is injected into the system (as heat or work), and energy leaves the system as work performed or heat dissipated. Thus, in either case, the standard formulation reflects a causal structure of input $\rightarrow$ response. However, the first law itself does not encode this directionality; it is an accounting principle and not a causal law. If the injection of energy depends on the system’s internal state, such as stress, deformation, or flux, then the causal loop becomes input $\rightarrow$ response $\rightarrow$ input. This unusual form of feedback does not violate the first law, as long as energy is conserved at each step. It simply means that the energy transfer into the system is regulated by its configuration. The first law remains valid under such feedback, because it governs balance, not cause.

The role of information. If the injection of energy depends on the state of a system, information (I) is necessarily involved, whether through explicit measurement or implicit sensing, and this information flow must be incorporated to maintain thermodynamic consistency. The system is no longer “autonomously driven,” and there is a hidden cost associated with the coupling between system observables and the injection of work. Thus, there must be a measurement, or sensing of a state, processing, and decision. For example, feedback control modifies the second law [142,143]. Analogous to feedback-controlled systems, the entropy production bound becomes

$$\langle W \rangle \leq -\Delta F + k_B T I, \quad (13)$$

where I is the mutual information between system and controller, and ΔF is the change in the free energy between the initial and final equilibrium states of the system. It quantifies the maximum amount of work that can be extracted from a system undergoing a transformation at constant temperature and volume, without feedback or information flow. Thus, to have feedback onto the energy injection, one must pay the

thermodynamic cost of acquiring and using that information, $k_B T I$ [Eq. (13)]. The second law is upheld if total entropy production, including effective information terms (associated with state-dependent coupling), is positive:

$$\dot{S}_{\text{tot}} = \dot{S}_{\text{system}} + \dot{S}_{\text{environment}} + \dot{S}_{\text{information}} \geq 0. \quad (14)$$

On the relationship between feedback, information, and variational principle. The unproductive (nonsliding) motions of myosin (pathways 0 and 1) consume high levels of ATP per unit time (as mechanical load is low). These behaviors may persist until more stable actomyosin configurations, such as antiparallel binding, are found (pathway 2), which costs lower levels of ATP per unit time (as mechanical load is high). In this sense, persistent pathway 0 and 1 motions are effectively performing a search for a lower-energy-state configuration, where the energetic cost is the number of ATPase cycles per unit time. The accumulated energy spent in pathways 0 and 1 may therefore reflect the energy associated with information, or feedback.

Furthermore, the transition from pathways 0 and 1 to pathway 2 is reminiscent of a variational principle in which the system has settled into an energetic optimum. However, a variational principle in driven systems is not universal and, if it exists at all, is likely context specific. Without it, however, the probability of certain configurational states of the system is unknown. What is currently understood about the probability of different states, and are these frameworks consistent with a state-dependent injection?

At the microscale, fluctuation theorems quantify how dissipation determines probability flows [144]. Specifically, fluctuation theorems such as the Jarzynski equality determine the probability of observing a certain amount of work in a forward process versus its reverse process [145,146]. However, fluctuation theorems do not yield a variational principle. They do not predict the steady state a system will settle into under continuous driving. Likewise, they do not favor one dissipative pathway or structure over another. By contrast, some have proposed that structures which dissipate energy efficiently are statistically favored under external driving [147] or that structures that absorb energy well tend to persist [148]. In this case, it is proposed that systems driven far from equilibrium can adapt dynamically and physically, by forming configurations that better absorb and dissipate energy from their environment. While there is a feedbacklike structure and adaptation can *emerge* statistically from dissipation-biased dynamics, the energy input protocol is not altered in response to the system's state. Thus, there is no explicit causal feedback of the system's mechanical state onto the protocol or energy injection in either of these frameworks.

Implications for active behaviors as energetic relaxations. Nonmonotonicity implies that there is a driven metastable state, which exists at higher energy, from which a system can relax. For example, cells accumulate mechanical energy via actomyosin contractility, confinement, or adhesion, creating a high-tension state. At some point (e.g., a signaling cue, threshold stress, local rupture, or stick-slip), this energy is rapidly released as a contraction, flow, or shape change [80,86,149,150]. These cell-level events can be seen as mechanical relaxations. Perhaps these relaxations, if the

distribution of their dissipated energies could be measured at the molecular scale, would also indicate SOC-like behavior. Indeed, it has been shown that modulation of Arp2/3 and formin nucleation determine the amount of myosin-based stress generated and ATP consumed [80–83]. This view re-frames certain physical behaviors of the cell as favorable pathways for dissipation, as a relaxation process arising from a dynamical metastability and potential near-criticality, as has been suggested in other systems [151–154].

On the connection between energy consumption and mechanical load. The coupling between load and energetics has a long precedent. In particular, the work of Fenn laid foundational principles in cellular metabolism and the energetics of muscle contraction. Fenn attached a weight to a frog muscle (sartorius), stimulating it electrically [155]. He then measured the heat production and mechanical work when comparing two cases: isometric contraction (when muscle generates force but does not shorten) and isotonic contraction (muscle shortens and lifts a load). In isotonic contractions, the total energy output (heat + work) is greater than in isometric contractions. Thus, force generation consumes more ATP when it results in motion (shortening) than when held isometrically. This work, described as the “Fenn effect,” established the idea of load-dependent energy metabolism. Thus, the Fenn effect reflects a fundamental principle that precedes and supports the thesis presented here: mechanical behavior and energy consumption are coupled, such that the energetic cost depends on the system's mechanical state.

A note on energetic efficiency. Unlike ordered actomyosin systems, as found in muscle, disordered systems can have a significantly lower energetic efficiency (<1%) [81]. In this sense, the amount of chemical energy consumed should be highly proportional to that which is dissipated, as comparatively little is invested in work. Thus, does efficiency (whether or not it is nonmonotonic) matter in biological systems? The answer may be both yes and no. Clearly, the creation of macromolecules, such as translation, is energetically expensive. However, when cells are performing principally mechanical tasks, is it possible that efficiency is limiting? While the steady-state mesenchymal-like migration may require approximately 1% of cell ATP [156], studies show that in contractile systems, such as platelets, in which there is no translation, it can be as high as 50% [157]. Separately, while overall ATP may not always be limiting, is it diffusion or reaction limited in the vicinity in which it is used?

Looking forward. As the calculation of entropy production rates are based on identifying select degrees of freedom, it is typically reflective of subsystem dynamics. As a result, observed fluxes in one subsystem may have counterfluxes in another, and thus nonmonotonicity at the system scale is uncertain. By contrast, direct methods of measuring dissipated energy reflect the total heat of the system, blind to subsystem dynamics, and thus the allocation of energy between systems (and therefore reciprocity) is unclear. Ideally, we desire to simultaneously measure local fluxes (e.g., EPR via imaging) with larger-scale fluxes of nucleotide (e.g., via NADH measurement [158,159] or even system-level measurements of heat (e.g., via calorimetry [141])). With these tools, we can unambiguously relate energy fluxes to broken reciprocity, allocation, pathway selection, and nonmonotonicity. Moreover,

developing methods to quantify energy fluxes at multiple scales may also provide a missing energetic complement to long-standing ideas that biological systems operate near dynamical instabilities or even critical points. Whereas current discussions of “living systems at the edge of instability” are grounded primarily in kinematic signatures, such as amplified fluctuations, sensitivity to perturbations, and scale-free correlations, the energetic underpinnings of these regimes remain largely unmeasured. If instabilities, excitability, or critical-like transitions indeed confer functional advantages, then they should also leave identifiable energetic fingerprints such as characteristic shifts in how work is allocated, how dissipation is routed, or how subsystem feedback alters the effective driving. Thus, simultaneous measurement of local and global energy fluxes may allow us to connect dynamical instability to its thermodynamic costs and benefits, revealing whether biological systems not only reside near such regimes but actively *exploit* their energetic structure to regulate assembly, adaptation, or decision-making.

III. CONCLUSIONS

In nonlinear systems, steady-state entropy production can exhibit local maxima or minima as the system reorganizes to

dissipate energy more (or less) efficiently (selecting between different pathways). This contrasts with linear response, where dissipation grows monotonically with forcing. In the case of the cell cytoskeleton, reorganization can include alterations to the geometric and mechanical parameters of the cell cytoskeleton, making the true injection of energy state dependent. Furthermore, feedback as yielding nonmonotonicity in the relationship between driving and EPR challenges the intuition that “more structured = more dissipative.” Finally, contractile behaviors can be interpreted as *relaxations* of energy. This can have dramatic implications for how biological systems determine structure, dynamics, and ultimately phenotypic outcomes.

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DATA AVAILABILITY

No data were created or analyzed in this study.

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