

Fluctuation-response design rules for nonequilibrium flows

Ying-Jen Yang ^{*}

Laufer Center for Physical and Quantitative Biology, Stony Brook University, Stony Brook, New York 11794, USA

Ken A. Dill 

*Laufer Center for Physical and Quantitative Biology, Stony Brook University, Stony Brook, New York 11794, USA;
Department of Physics, Stony Brook University, Stony Brook, New York 11794, USA;
and Department of Chemistry, Stony Brook University, Stony Brook, New York 11794, USA*



(Received 21 February 2026; accepted 18 August 2026; published 13 October 2026)

Biomolecular machines operate as stochastic flows on networks. Here, we develop a principled approach to *network design* where local transition rates are systematically tuned to achieve global dynamical objectives. Based on the fluctuation-response duality in caliber force theory, our formalism unifies existing nonequilibrium response relations under a single conjugate structure. Topologically, a force-rate Jacobian yields response symmetries that establish a local orthogonal control protocol for network flows. Analytically, it parses covariance to diagnose noise mechanisms, revealing the transition from timing to branching fluctuations in a kinesin motor. With algebraic closure streamlining multiobjective gradient evaluations, this framework provides a unified blueprint for designing stochastic dynamics.

DOI: [10.1103/g8rc-615y](https://doi.org/10.1103/g8rc-615y)

I. INTRODUCTION

Consider a stochastic dynamical process transitioning among a network of states. In biophysics alone, such stochastic network flows are involved in the molecular mechanisms of motors and pumps [1–3], ultrasensitive switches in flagella [4,5], the catalytic and allosteric actions in enzymes [6–9], phosphorylation cycles [10,11], energy and chemical transduction [12,13], and others. A fundamental goal is to control the long-term statistics of flows, given the local transition rates.

While Markov state models and master equations describe these dynamics [14], they do not prescribe design. What is missing are principles for the optimization, control, and evolution of network flows: How should one systematically tune local transition rates to achieve specific global functions? Mathematically, this requires solving the response gradient—knowing exactly how local perturbations shift the long-term stochastic dynamics. However, raw gradients evaluated case by case do not reveal general principles. To navigate systematically, we exploit a key physical connection: General response relations are encoded in the system’s fluctuations.

Echoing Onsager’s regression hypothesis, recent nonequilibrium (NEQ) advances have established diverse fluctuation-response equalities and bounds [15–30], revealing that “noisier” mechanisms are inherently more susceptible to perturbative control. However, operationalizing these insights

for systematic NEQ flow design faces some obstacles. First, design requires exact gradients, not just bounds. While inequalities establish rigorous sensitivity limits, optimization and control require directional derivatives to navigate parameter space. Second, exact response equalities remain mathematically fragmented into isolated identities. While many response relations have been derived by various powerful mathematics, a unifying framework for systematic design is lacking. Third, gradient evaluations for composite objectives require query-specific formulations. Optimizing a biochemical reaction network typically requires the simultaneous tuning of multiple targets—such as the means and variances of state distributions or fluxes. Conventional analytical approaches evaluate these by defining and differentiating separate state-space operators for each specific objective. This repetitive setup creates an implementation overhead for multiobjective network design. We need an actionable framework that evaluates these diverse gradients through a single, unified structure.

Here, we address this need using caliber force theory (CFT) [31] to construct a unifying fluctuation-response framework with a thermodynamic-like structure. Analytically, this approach connects the fragmented zoo of NEQ response equalities through conjugate relations between distribution and flux observables and their path entropic forces. We derive a response-inverse-matrix (RIM) relation based on the force-rate Jacobian matrix that reveals new topological constraints—node, edge, and cycle symmetries—for orthogonal network control. Computationally, it evaluates the exact gradients of means and variances simultaneously across all types of observables, eliminating the need for query-specific setups. In practice, we apply the framework to a data-fitted kinesin model [2]. Deriving a universal rule that a transition aligned with the net flux contributes at least as much as its

^{*}Contact author: ying-jen.yang@stonybrook.edu

reversal, we parse the motor's internal fluctuations to reveal the chemomechanical couplings driving its load-dependent noise transition. This framework provides a road map for gradient-based design.

II. THEORETICAL FRAMEWORK

Our foundation here is CFT, a dynamical variational formalism based on maximum caliber [32,33] that *mirrors* the conjugate structure of equilibrium (EQ) thermodynamics in nonequilibria [31]. We begin by considering the *path entropy* of Markov jump processes—defined as the logarithm of path probability ratio, $\ln(\mathcal{P}_{\mathbf{k}}/\mathcal{P}_{\mathbf{u}})$. It measures the pathwise entropic cost of driving a unit-rate reference process $\mathbf{u}$ to the dynamics with transition rate $\mathbf{k}$. For a path ω_t with duration t , it can be expressed in terms of *counting observables* [34]:

$$\ln \frac{\mathcal{P}_{\mathbf{k}}(\omega_t)}{\mathcal{P}_{\mathbf{u}}(\omega_t)} = \sum_{i \neq j} N_{ij}(\omega_t) \ln k_{ij} - \sum_i T_i(\omega_t) \varepsilon_i(\mathbf{k}), \quad (1)$$

where N_{ij} is the number of transitions $i \rightarrow j$, T_i is the total dwell time of state i , and $\varepsilon_i = \sum_{j(\neq i)} (k_{ij} - 1)$ is the excess escape rate relative to the unit-rate reference. However, these raw observables have undesirable redundancies. Conservation laws—time additivity $\sum_i T_i = t$ and Kirchhoff's current balance $\sum_{j(\neq i)} N_{ij} \sim \sum_{j(\neq i)} N_{ji}$ [35]—enforce strong coupling among them in the long term, rendering the naive counts (N_{ij} , T_i) degenerate axes for control.

CFT resolves this redundancy by identifying the *asymptotically orthogonal* counting variables $\mathbf{X}$ and their conjugate variables $\mathfrak{F}$ [31,34]:

$$\ln \frac{\mathcal{P}_{\mathbf{k}}(\omega_t)}{\mathcal{P}_{\mathbf{u}}(\omega_t)} \sim \mathfrak{F}(\mathbf{k}) \cdot \mathbf{X}(\omega_t) - \mathfrak{c}(\mathbf{k}) t, \quad (2)$$

where the caliber rate $\mathfrak{c} = \sum_{j \neq m} (k_{mj} - 1)$ plays a role in NEQ processes analogous to the role free energy plays for EQ systems—as the logarithm of the dynamic partition function that generates observable statistics from their partial derivatives [31,34]. The vector $\mathbf{X} = (\Phi_{ij}, T_n, \Psi_c)$ is a complete observable basis consistent with the asymptotic constraints: (1) edge traffic $\Phi_{ij} = N_{ij} + N_{ji}$; (2) dwell times T_n (excluding a reference m); and (3) cycle net fluxes $\Psi_c = N_{ab} - N_{ba}$, defined by the net flux across the chord ab of a fundamental cycle c [36] (mnemonic: the time-irreversible counterpart to traffic, $\Psi \equiv \text{"i"} + \Phi$). Dividing by time gives their rates $\mathbf{x} = (\phi_{ij}, f_n, \psi_c)$, and taking steady-state averages yields the intensive rate coordinate for the parameter space $\langle \mathbf{x} \rangle = \langle \mathbf{X} \rangle / t = (\tau_{ij}, \pi_n, J_c)$.

The variables $\mathfrak{F}$ are the derivatives of average path entropy rate, $\mathfrak{s}_{\text{path}} = -\sum_{\omega} \mathcal{P}_{\mathbf{k}}(\omega) \ln[\mathcal{P}_{\mathbf{k}}(\omega)/\mathcal{P}_{\mathbf{u}}(\omega)]$, and thus can be understood as *path entropic forces* [31]. Their explicit transition-rate expressions reveal their physical roles:

$$\begin{aligned} \mathfrak{F}_{\text{edge}, ij} &= -\frac{\partial \mathfrak{s}_{\text{path}}}{\partial \tau_{ij}} = \frac{1}{2} \ln k_{ij} k_{ji}, \\ \mathfrak{F}_{\text{node}, n} &= -\frac{\partial \mathfrak{s}_{\text{path}}}{\partial \pi_n} = \sum_{i(\neq m)} (k_{mi} - 1) - \sum_{j(\neq n)} (k_{nj} - 1), \\ \mathfrak{F}_{\text{cycle}, c} &= -\frac{\partial \mathfrak{s}_{\text{path}}}{\partial J_c} = \frac{1}{2} \ln \frac{k_{i_0 i_1} k_{i_1 i_2} \cdots k_{i_{\sigma} i_0}}{k_{i_0 i_{\sigma}} k_{i_{\sigma} i_{\sigma-1}} \cdots k_{i_1 i_0}}, \end{aligned} \quad (3)$$

where $i_0, i_1, i_2, \dots, i_{\sigma}, i_0$ is the state sequence of cycle c . With the unit-rate process chosen as the zero-force reference, these edge, node, and cycle forces are the drives pushing the process to deviate from unit transition activity and break the uniform symmetry of state distribution and detailed balance symmetry of net fluxes, respectively. These are purely dynamical, entropy-based constructs, conceptually distinct from traditional energy-based thermodynamic forces (such as reservoir free-energy differences), although the cycle forces seamlessly map to them when local detailed balance is assumed for molecular machines (cycle force is half of cycle affinity in stochastic thermodynamics).

The path entropic forces $\mathfrak{F}$ and the distribution-flux observables $\mathbf{X}$ are formally conjugate with relations identical to those in EQ thermodynamics [31]. CFT thus establishes the maximum caliber and large deviation conjugacy to the thermodynamic driving forces (cycle affinities) in stochastic thermodynamics. Most notably, they exhibit a fundamental conjugacy between *observable fluctuations* and their corresponding *force responses*: The average susceptibility of a CFT rate observable x_{α} to a force $\mathfrak{F}_{\beta}$ —while holding all other forces fixed—is exactly their asymptotic covariance [31]:

$$\left. \frac{\partial \langle x_{\alpha} \rangle}{\partial \mathfrak{F}_{\beta}} \right|_{\mathfrak{F}_{\gamma \neq \beta}} = \frac{\partial^2 \mathfrak{c}(\mathfrak{F})}{\partial \mathfrak{F}_{\alpha} \partial \mathfrak{F}_{\beta}} = \lim_{t \rightarrow \infty} t \text{Cov}[x_{\alpha}, x_{\beta}]. \quad (4)$$

Thus, fluctuations equal susceptibilities: (1) The strictly positive variance implies *monotonic* force responses: Just as heat capacity is positive, any average rate observable $\langle x_{\alpha} \rangle \in \{\tau_{ij}, \pi_n, J_c\}$ must increase with its own conjugate drive $\mathfrak{F}_{\alpha}$. (2) The symmetry of covariance enforces a *Maxwell-Onsager-like reciprocity* far from equilibrium [37]: The susceptibility of observable $\langle x_{\alpha} \rangle$ to force $\mathfrak{F}_{\beta}$ is identical to the response of $\langle x_{\beta} \rangle$ to force $\mathfrak{F}_{\alpha}$.

Equation (4) demonstrates how to restore reciprocity in NEQ responses: It requires a *global* rate tuning that fixes all other entropic forces [38]. For example, as the cycle force equals the reservoir free-energy drive under local detailed balance, the cross-cycle flux-force response offers one such far-from-equilibrium generalization of Onsager reciprocity—restored not by tuning the reservoir alone, but through the coordinated rate adjustment that holds all other entropic forces fixed (see Sec. II C of the Supplemental Material for a demonstration [34]). Under typical local rate perturbations—tuning a single rate k_{ij} while holding other rates fixed—the intrinsic reciprocity is screened out by the chain rule through a force-rate Jacobian mapping $\mathbf{A}_{(ij), \beta} \equiv \partial \mathfrak{F}_{\beta} / \partial \ln k_{ij}$ (Fig. 1):

$$\left. \frac{\partial \langle \mathbf{x} \rangle}{\partial \ln k_{ij}} \right|_{k_{ab}, ab \neq ij} = \sum_{\beta} \frac{\partial \langle \mathbf{x} \rangle}{\partial \mathfrak{F}_{\beta}} \frac{\partial \mathfrak{F}_{\beta}}{\partial \ln k_{ij}}. \quad (5)$$

This explains why response reciprocity appears broken under rate perturbations of NEQ dynamics.

The Jacobian matrix $\mathbf{A}$ not only elucidates this apparent symmetry breaking but structurally encodes all fluctuations and responses. Utilizing the force-rate relations in Eq. (3) yields the RIM relation [34]:

$$\frac{\partial \langle x_{\alpha} \rangle}{\partial \ln k_{ij}} = \lim_{t \rightarrow \infty} t \times \text{Cov}[x_{\alpha}, \lambda_{ij}] = \pi_i k_{ij} [\mathbf{A}^{-1}]_{\alpha, (ij)}, \quad (6)$$

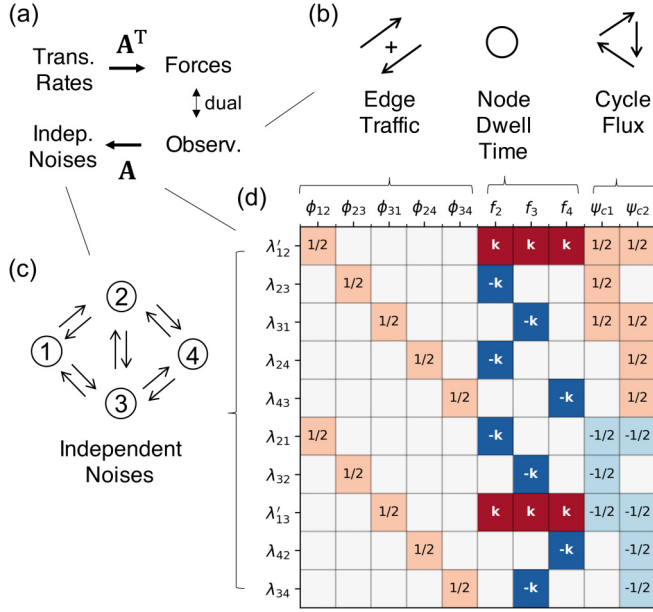


FIG. 1. The sparse structure of fluctuation-response duality. (a) The Jacobian matrix $\mathbf{A}$ acts as the bridge between stochasticity and control: It maps physical observables $\mathbf{x}$ to independent noise sources λ (fluctuation structure), while simultaneously linking transition rates $\ln \mathbf{k}$ to conjugate forces $\mathfrak{F}$ (response structure). (b) The complete observable basis: edge traffic ϕ_{ij} , node frequency f_n , and cycle net flux ψ_c . (c) A representative four-state network showing that every transition edge generates an intrinsic independent noise source λ_{ij} . (d) The explicit structure of the Jacobian $\mathbf{A}$ for the four-state example. The symbol k (or $-k$) denotes the transition rate k_{ij} corresponding to the specific row index. The prime notation λ'_{mj} denotes the shifted noise source $\lambda'_{mj} = \lambda_{mj} + k_{mj}$ for transitions leaving the reference state $m = 1$. White squares denote zeros.

where the inverse matrix $\mathbf{A}^{-1} = \nabla_{\mathfrak{F}} \ln \mathbf{k}(\mathfrak{F})$ is itself the reverse Jacobian of this coordinate mapping. Here, $\lambda_{ij} = (N_{ij} - k_{ij}T_i)/t$ are the compensated jump-count rates [27,30,39], which possess diagonal asymptotic covariances $t \times \text{Cov}[\lambda_{ij}, \lambda_{mn}] \sim \pi_i k_{ij} \delta_{i,m} \delta_{j,n}$ and act as independent noise sources at each transition. These noise sources are linearly spanned by the CFT observables: $\lambda[\omega_i] \sim \mathbf{A}(\mathbf{k}) \mathbf{x}[\omega_i] - \nabla_{\ln \mathbf{k}} \mathbf{c}(\mathbf{k})$.

While the first equality in Eq. (6) is well known [16,27,30], and inverting the transition rate matrix is a standard way to derive response relations [24,40,41], $\mathbf{A}^{-1}$ is unique as a topological Jacobian mapping between transition rates and path entropic forces. This mapping exposes the observable-force conjugate structure underlying the first equality. In the following sections, we demonstrate how this yields three main results: (1) It operationalizes a known fluctuation decomposition [26–29,42] into a mechanistic diagnoser, parsing the fluctuation landscape to pinpoint dominant noise contributors; (2) it unifies various isolated fluctuation-response relations [19,20,24–26,28,43] under the overarching topological constraints of $\mathbf{A}^{-1}\mathbf{A} = \mathbf{I}$, establishing an orthogonal control protocol; and (3) the algebraic closure of the Jacobian matrix bypasses query-specific setups, streamlining multiobjective gradient evaluations for locally connected networks.

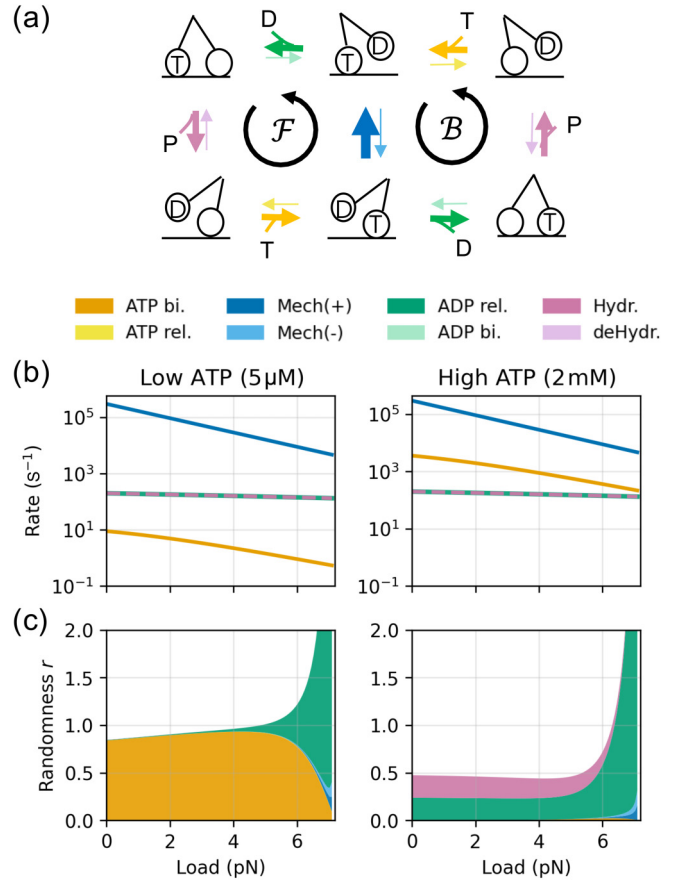


FIG. 2. Dissecting a molecular motor's randomness. (a) The six-state model for kinesin [2]. (b) The bigger the load that the motor has to pull, the slower it runs, for given ATP energy sources [2]. (c) Decomposition of the motor's randomness parameter r . The total randomness is decomposed into contributions from functional groups (aggregating forward $\mathcal{F}$ and backward $\mathcal{B}$ cycles), represented by the stacked areas. The upper boundary of the stacked areas is the randomness calculated by the kinesin model, fitted to Ref. [44]. The motor becomes inefficient when pulling heavy loads.

III. FLUCTUATION DECOMPOSITION IS A MECHANISTIC DIAGNOSER

We first use RIM to recover a known asymptotic covariance decomposition [26–29] and show how to operationalize this theoretical result to reveal the dynamical coupling schemes within biochemical reaction networks.

The total covariance between any two observables $x, x' \in (\phi_{ij}, f_n, \psi_c)$ can be decomposed into a sum over their projections onto independent transition noise axes [26–29,34]:

$$\text{Cov}[x, x'] \sim \sum_{i,j} \text{Cov}[x, \hat{\lambda}_{ij}] \times \text{Cov}[x', \hat{\lambda}_{ij}], \quad (7)$$

where $\hat{\lambda}_{ij} = \lambda_{ij}/\sqrt{\pi_i k_{ij}/t}$ is the unit-variance noise source at transition $i \mapsto j$. Geometrically, this decomposition reflects the inner product projection rule for vectors: $\mathbf{u} \cdot \mathbf{v} = \sum_z (\mathbf{u} \cdot \hat{\mathbf{e}}_z)(\mathbf{v} \cdot \hat{\mathbf{e}}_z)$. We use this to dissect the diffusivity of a kinesin molecular motor, modeled by a data-fitted six-state network [Fig. 2(a)] [2]. Defining a randomness parameter r as the variance-to-mean ratio of the net mechanical stepping rate

$\psi = (N_+ - N_-)/t$ (where $N_{\pm}$ are the forward and backward step counts), this randomness expands into a sum over the local network sensitivities:

$$r = \lim_{t \rightarrow \infty} \frac{t \times \text{Var}(\psi)}{\langle \psi \rangle} = \lim_{t \rightarrow \infty} \frac{1}{\langle \psi \rangle} \sum_{i,j} t (\text{Cov}[\psi, \hat{\lambda}_{ij}])^2$$

$$= \frac{1}{\langle \psi \rangle} \sum_{i,j} \underbrace{\frac{k_{ij}}{\pi_i} \left(\frac{\partial \langle \psi \rangle}{\partial k_{ij}} \right)^2}_{\text{Sensitivity } S_{ij}}. \quad (8)$$

Because the noise contribution scales with the squared sensitivity $(\partial \langle \psi \rangle / \partial k_{ij})^2$, a transition strongly coupled to the mechanical stepping inherently amplifies its intrinsic noise into the long-term stepping fluctuation. This decomposition itself is known [26–29]; RIM evaluates it systematically, computing all terms simultaneously via $\mathbf{A}^{-1}$.

The randomness decomposition under different loads and ATP concentrations is shown in Figs. 2(b) and 2(c). Across different conditions and within each forward/reverse edge pair, the transition opposing the net flux never contributes more noise than its forward counterpart (equality only when the edge is locally balanced, $\pi_i k_{ij} = \pi_j k_{ji}$). Using RIM, we show that this is a generic, system-independent asymmetry: The sensitivity contribution of a forward step (aligned with the net flux) is at least as large as that of the reversal, as it scales proportionally with the local one-way flux: $S_{ij}/S_{ji} = (\pi_i k_{ij})/(\pi_j k_{ji})$ [45]. Because each group in Fig. 2(c) aggregates a set of forward edges against the reversals of exactly those edges, the pairwise inequality sums to the same statement at group level.

The diagnostic power of this decomposition is further illustrated by a physical insight into how the kinesin motor “wastes time”—either by getting stuck at rate-limiting steps or by bifurcating into backward cycles. Figures 2(b) and 2(c) reveal a load-dependent shift in the motor’s scheme: (1) At low loads (far from stalling, on the left), randomness is dominated by *timing noise*. The motor wastes time waiting for the slowest forward reaction—which is also the dominant fluctuation contributor—to happen, such as ATP arrival at low [ATP] or ADP release and hydrolysis at high [ATP]. (2) At high loads (near the stall force, on the right), the mechanism shifts to *branching noise*. As the heavy load makes the backward mechanical rate comparable to the forward rate, the motor wastes time taking the wrong turns. The ADP release step now dominates the randomness because it acts as the critical kinetic crossroad partitioning the forward and backward cycles. This mechanistic transition—from temporal variance (waiting for a step to occur) to topological variance (committing to a directional branch)—demonstrates how dynamical coupling schemes are encoded within the covariance-sensitivity decomposition.

In contrast to thermodynamic uncertainty relations that bound the overall magnitude of randomness based on global dissipation [46–48], we show that this decomposition—efficiently evaluated via our framework—pinpoints the specific transitions driving the motor’s stochastic behavior.

IV. CFT UNIFIES FLUCTUATION-RESPONSE RELATIONS AND DERIVES LOCAL ORTHOGONAL CONTROL PROTOCOLS

The Jacobian matrix $\mathbf{A}$ connects the thermodynamic-like conjugate relations [Eq. (4)] to the transition rate responses of distributions and fluxes $\langle x \rangle \in \{\tau_{ij}, \pi_n, J_c\}$. This reveals that many existing response relations [19,20,24–26,28,43] correspond simply to extracting specific columns and rows from the identity $\mathbf{A}^{-1}\mathbf{A} = \mathbf{I}$. We summarize these connections below and demonstrate how these unifying symmetries prescribe a local orthogonal control protocol. Derivations are provided in Sec. IV of the Supplemental Material [34].

On each edge ij , there is an edge reciprocity:

$$\frac{1}{\pi_i} \frac{\partial \langle x \rangle}{\partial k_{ij}} + \frac{1}{\pi_j} \frac{\partial \langle x \rangle}{\partial k_{ji}} = 2\delta_{\langle x \rangle, \tau_{ij}}. \quad (9)$$

Applied to Arrhenius rate models, this relation governs perturbations to the symmetric barrier height B_{ij} ($\partial_{B_{ij}} \equiv -k_{ij}\partial_{k_{ij}} - k_{ji}\partial_{k_{ji}}$). The case of $\langle x \rangle = \pi$ was recently reported by Bebon and Speck [43], with other variables derivable from it. This symmetry also recovers a universal constraint shown by Aslyamov and Esposito [25]: The barrier response of any observable $\langle x \rangle \neq \tau_{ij}$ is proportional to the unperturbed net flux $J_{ij} := \pi_i k_{ij} - \pi_j k_{ji}$, yielding $\partial_{B_{ij}} \langle x \rangle = -(J_{ij}/\pi_i)\partial_{k_{ij}} \langle x \rangle$. Consequently, barrier perturbations cannot tune distributions π_n or distant fluxes if the perturbed edge is locally equilibrated ($J_{ij} = 0$); they acquire control authority only through a nonequilibrium net flux. The symmetry can also be used to give physical explanations of the inequalities derived in Ref. [25] (see Sec. IV G of the Supplemental Material [34]).

On each node n , there is a node escaping symmetry:

$$\sum_{l(\neq m)} \frac{k_{ml}}{\pi_m} \frac{\partial \langle x \rangle}{\partial k_{ml}} - \sum_{j(\neq n)} \frac{k_{nj}}{\pi_n} \frac{\partial \langle x \rangle}{\partial k_{nj}} = \delta_{\langle x \rangle, \pi_n}. \quad (10)$$

When applied to Arrhenius rate models, this symmetry encapsulates perturbations to the site energy E_n ($k_{nj} \propto e^{E_n}$), scaling all outgoing rates simultaneously ($\partial_{E_n} \equiv \sum_{j(\neq n)} k_{nj}\partial_{k_{nj}}$). By applying scale homogeneity, this recovers the state distribution response relations [20]. When applied to fluxes, it restores recent generalizations [19,24] showing that energy-well perturbations scale network flows proportionally to local occupancy ($\partial_{E_n} \tau_{ij} = \pi_n \tau_{ij}$ and $\partial_{E_n} J_c = \pi_n J_c$).

On each cycle c , there is a cycle symmetry:

$$\sum_{ij \in c^+} \frac{1}{\pi_i} \frac{\partial \langle x \rangle}{\partial k_{ij}} - \sum_{ji \in c^-} \frac{1}{\pi_j} \frac{\partial \langle x \rangle}{\partial k_{ji}} = 2\delta_{\langle x \rangle, J_c}. \quad (11)$$

This enforces a new topological constraint: The cumulative sensitivity along any forward cycle must precisely balance that of its reversal (for observables $\langle x \rangle \neq J_c$, including all π_n, τ_{ij} , and the other cycle fluxes $J_{c'}$). For observables other than the edge traffics on cycle c , it can be rewritten in terms of the antisymmetric rate perturbation $\partial_{F_{ij}} \equiv \frac{1}{2}(k_{ij}\partial_{k_{ij}} - k_{ji}\partial_{k_{ji}})$ [20,26]:

$$\sum_{ij \in c^+} \frac{2}{\tau_{ij}} \frac{\partial \langle x \rangle}{\partial F_{ij}} = \delta_{\langle x \rangle, J_c}. \quad (12)$$

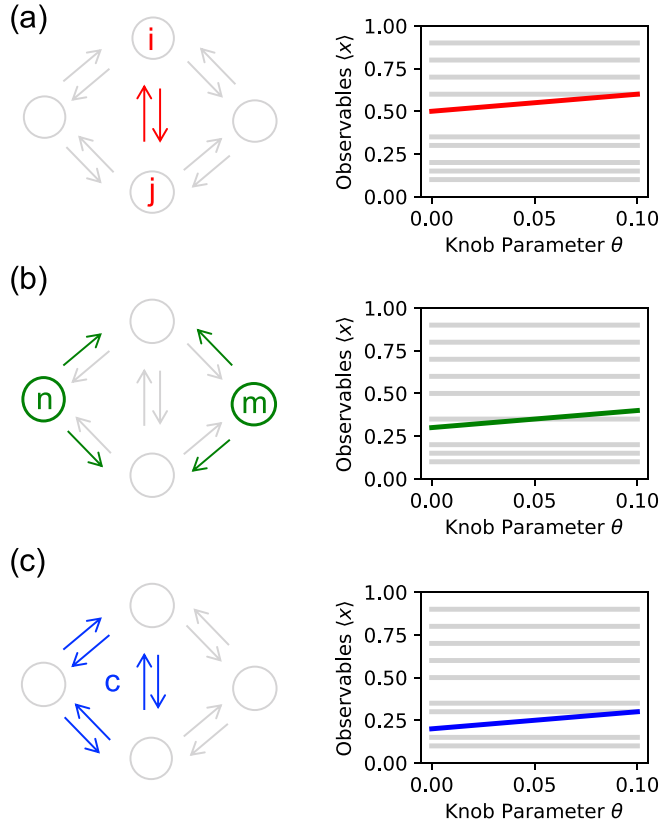


FIG. 3. CFT response symmetries realize local orthogonal control of nonequilibrium flows. (a) Edge symmetry in Eq. (9) isolates a local edge traffic τ_{ij} (red). (b) Node symmetry in Eq. (10) isolates a target state probability π_n (green). (c) Cycle symmetry in Eq. (11) isolates a fundamental cycle flux J_c (blue). In each protocol, applying the local rate perturbations (via the knob parameter θ properly scaling rates based on local π) precisely tunes the target variable while leaving all other CFT observables ($\pi_{n'}, \tau_{i'j'}, J_{c'}$) invariant (gray horizontal lines).

Notably, this constraint revealed by CFT structurally resembles the flux control summation theorem in metabolic control analysis [49,50].

Typically, perturbing a single transition rate triggers cascading changes across the entire network. These response symmetries, instead, prescribe a “quarantined” conservative tuning for distributions and flows: a localized orthogonal control scheme that tunes a single target variable while keeping all others fixed [51]. As illustrated in Fig. 3, this operates on two levels: isolating the target from the rest of the network and decoupling variables within the target itself.

(1) Edge reciprocity isolates local traffic by symmetrically tuning a pair of rates with $\partial k_{ij}/\partial\theta = 1/(2\pi_i)$ and $\partial k_{ji}/\partial\theta = 1/(2\pi_j)$. This not only isolates the edge but also ensures the internal net flux and the connecting node distributions remain fixed.

(2) Node escaping symmetry isolates a change in state probability π_n by scaling its escaping rates k_{nl} via the chain-rule factor $\partial k_{nl}/\partial\theta = -k_{nl}/\pi_n$ (and the reference node m in the opposite way). This keeps all outgoing net fluxes invariant, localizing the perturbation.

(3) Cycle symmetry isolates a cycle flux by applying antisymmetric perturbations weighted by $1/(2\pi)$ along a closed loop. This isolates probability transport within the cycle that also leaves the internal state probabilities and edge traffic on the cycle unchanged.

A single-variable change can also be realized via CFT’s observable coordinates: $k_{ij} = (\tau_{ij} + J_{ij})/(2\pi_i)$, but such tuning requires global network adjustments. The response symmetries derived here instead establish a strictly local orthogonal control protocol for NEQ flows.

V. IMPLEMENTATION UNIFORMITY FOR MULTIOBJECTIVE DESIGN

Optimizing reaction networks requires evaluating exact gradients of multiple objectives, such as the randomness parameter r . Because the CFT Jacobian matrix scales with the number of edges, its inversion carries a dimensionality cost that scales less favorably than state-space analytical methods, such as the Drazin inverse, in dense networks. However, for sparse, locally connected networks typical of biophysical systems, CFT achieves near-linear scaling comparable to that of the Drazin inverse ($\mathcal{O}(N^{1.3})$ versus $\mathcal{O}(N^{1.1})$). While slightly slower in absolute computational time (see Sec. V of the Supplemental Material for detailed benchmarks [34]), the practical benefit of the CFT method is implementation uniformity for multiobjective design [52]. Traditional approaches require deriving and coding distinct state-space operators for each new target observable. In contrast, CFT’s algebraic closure ($\partial\mathbf{A}^{-1} = -\mathbf{A}^{-1}(\partial\mathbf{A})\mathbf{A}^{-1}$) allows a single matrix inversion to simultaneously evaluate gradients of means and variances across the entire observable basis, bypassing repetitive calculus.

VI. CONCLUSIONS

We use path entropic forces to unify nonequilibrium fluctuation-response relations. This conjugate structure parses covariance to diagnose network noise mechanisms and yields topological symmetries unifying response relations and prescribing local orthogonal controls. With implementation uniformity and its thermodynamics-like two-law foundation [31], the framework provides a principled blueprint for designing stochastic flows.

ACKNOWLEDGMENTS

We are grateful for the financial support from the Laufer Center for Physical and Quantitative Biology at Stony Brook, the John Templeton Foundation (Grant No. 62564), and NIH (Grant No. RM1-GM135136). This material is based upon work supported by the Defense Advanced Research Projects Agency (DARPA).

The views and conclusions contained in this document are those of the authors and should not be interpreted as representing the official policies, either expressed or implied, of the U.S. Government. Distribution Statement “A” (Approved for Public Release, Distribution Unlimited).

DATA AVAILABILITY

The data that support the findings of this article are openly available [55].

- [1] A. B. Kolomeisky and M. E. Fisher, Molecular motors: A theorist's perspective, *Annu. Rev. Phys. Chem.* **58**, 675 (2007).
- [2] S. Liepelt and R. Lipowsky, Kinesin's network of chemo-mechanical motor cycles, *Phys. Rev. Lett.* **98**, 258102 (2007).
- [3] J. A. Wagoner and K. A. Dill, Mechanisms for achieving high speed and efficiency in biomolecular machines, *Proc. Natl. Acad. Sci. USA* **116**, 5902 (2019).
- [4] T. A. J. Duke, N. Le Novère, and D. Bray, Conformational spread in a ring of proteins: A stochastic approach to allostery, *J. Mol. Biol.* **308**, 541 (2001).
- [5] Y. Tu, The nonequilibrium mechanism for ultrasensitivity in a biological switch: Sensing by Maxwell's demons, *Proc. Natl. Acad. Sci. USA* **105**, 11737 (2008).
- [6] J. Monod, J. Wyman, and J.-P. Changeux, On the nature of allosteric transitions: A plausible model, *J. Mol. Biol.* **12**, 88 (1965).
- [7] J. J. Hopfield, Kinetic proofreading: A new mechanism for reducing errors in biosynthetic processes requiring high specificity, *Proc. Natl. Acad. Sci. USA* **71**, 4135 (1974).
- [8] J. Ninio, Kinetic amplification of enzyme discrimination, *Biochimie* **57**, 587 (1975).
- [9] H. Qian and E. L. Elson, Single-molecule enzymology: Stochastic Michaelis–Menten kinetics, *Biophys. Chem.* **101–102**, 565 (2002).
- [10] A. Goldbeter and D. E. Koshland, An amplified sensitivity arising from covalent modification in biological systems, *Proc. Natl. Acad. Sci. USA* **78**, 6840 (1981).
- [11] H. Qian, Phosphorylation energy hypothesis: Open chemical systems and their biological functions, *Annu. Rev. Phys. Chem.* **58**, 113 (2007).
- [12] T. L. Hill, *Free Energy Transduction and Biochemical Cycle Kinetics* (Springer, New York, 1989).
- [13] A. I. Brown and D. A. Sivak, Theory of nonequilibrium free energy transduction by molecular machines, *Chem. Rev.* **120**, 434 (2020).
- [14] J. Schnakenberg, Network theory of microscopic and macroscopic behavior of master equation systems, *Rev. Mod. Phys.* **48**, 571 (1976).
- [15] M. Baiesi, C. Maes, and B. Wynants, Fluctuations and response of nonequilibrium states, *Phys. Rev. Lett.* **103**, 010602 (2009).
- [16] U. Seifert and T. Speck, Fluctuation-dissipation theorem in nonequilibrium steady states, *Europhys. Lett.* **89**, 10007 (2010).
- [17] A. C. Barato and R. Chetrite, A formal view on level 2.5 large deviations and fluctuation relations, *J. Stat. Phys.* **160**, 1154 (2015).
- [18] B. Altaner, M. Poletti, and M. Esposito, Fluctuation-dissipation relations far from equilibrium, *Phys. Rev. Lett.* **117**, 180601 (2016).
- [19] J. D. Mallory, A. B. Kolomeisky, and O. A. Igoshin, Kinetic control of stationary flux ratios for a wide range of biochemical processes, *Proc. Natl. Acad. Sci. USA* **117**, 8884 (2020).
- [20] J. A. Owen, T. R. Gingrich, and J. M. Horowitz, Universal thermodynamic bounds on nonequilibrium response with biochemical applications, *Phys. Rev. X* **10**, 011066 (2020).
- [21] G. Fernandes Martins and J. M. Horowitz, Topologically constrained fluctuations and thermodynamics regulate nonequilibrium response, *Phys. Rev. E* **108**, 044113 (2023).
- [22] J. A. Owen and J. M. Horowitz, Size limits the sensitivity of kinetic schemes, *Nat. Commun.* **14**, 1280 (2023).
- [23] K. Ptaszyński, T. Aslyamov, and M. Esposito, Dissipation bounds precision of current response to kinetic perturbations, *Phys. Rev. Lett.* **133**, 227101 (2024).
- [24] T. Aslyamov and M. Esposito, General theory of static response for Markov jump processes, *Phys. Rev. Lett.* **133**, 107103 (2024).
- [25] T. Aslyamov and M. Esposito, Nonequilibrium response for Markov jump processes: Exact results and tight bounds, *Phys. Rev. Lett.* **132**, 037101 (2024).
- [26] T. Aslyamov, K. Ptaszyński, and M. Esposito, Nonequilibrium fluctuation-response relations: From identities to bounds, *Phys. Rev. Lett.* **134**, 157101 (2025).
- [27] J. Zheng and Z. Lu, Unified linear fluctuation-response theory arbitrarily far from equilibrium, *Phys. Rev. E* **112**, 064103 (2025).
- [28] K. Ptaszyński, T. Aslyamov, and M. Esposito, Nonequilibrium fluctuation-response relations for state observables, *Phys. Rev. E* **113**, 024130 (2026).
- [29] K. Ptaszyński, T. Aslyamov, and M. Esposito, Nonequilibrium fluctuation-response relations for state-current correlations, *Phys. Rev. E* **113**, 024131 (2026).
- [30] L. T. Stutzer, C. Dieball, and A. Godec, Stochastic calculus for pathwise observables of Markov-jump processes: Unification of diffusion and jump dynamics, *Phys. Rev. X* **16**, 021038 (2026).
- [31] Y.-J. Yang and K. A. Dill, A principled basis for nonequilibrium network flows, *Nat. Commun.* **17**, 4980 (2026).
- [32] E. T. Jaynes, The minimum entropy production principle, *Annu. Rev. Phys. Chem.* **31**, 579 (1980).
- [33] S. Pressé, K. Ghosh, J. Lee, and K. A. Dill, Principles of maximum entropy and maximum caliber in statistical physics, *Rev. Mod. Phys.* **85**, 1115 (2013).
- [34] See Supplemental Material at <http://link.aps.org/supplemental/10.1103/g8rc-615y> for more details, which includes Refs. [53,54].
- [35] We use standard asymptotic analysis notation $a \sim b$ to represent asymptotic equivalency, $\lim_{t \rightarrow \infty} a(t)/b(t) = 1$.
- [36] Net flux must be cyclic at steady state because total flow into a state must equal the outward flow. Fundamental cycle is a graph-theoretic method to find a linearly independent set of cycle fluxes, by choosing a spanning tree and adding back edges (chords) one by one to define the cycles. See Sec. IB in the Supplemental Material [34] for an example and Refs. [12,14,31] for more details.
- [37] We use the suffix “-like” as a formal analogy: Mathematically, this is the Hessian symmetry of the caliber in CFT conjugate coordinates, generally distinct from Onsager reciprocity among experimentally tunable parameters. In the special case of cycle forces under local detailed balance, however, $\mathfrak{F}_{\text{cycle}}$ coincides with the reservoir free-energy drive, so this symmetry does reduce to a genuine far-from-equilibrium generalization of Onsager reciprocity—restorable, though, only via the coordinated global tuning demonstrated in Sec. IIC in the Supplemental Material [34], not by adjusting the reservoir alone.
- [38] This can be seen by evaluating $\mathbf{k}(\mathfrak{F})$ following Ref. [31].
- [39] E. Kwon and J. S. Lee, A unified framework for classical and quantum uncertainty relations using stochastic representations, *Commun. Phys.* **8**, 444 (2025).

- [40] S. E. Harvey, S. Lahiri, and S. Ganguli, Universal energy-accuracy tradeoffs in nonequilibrium cellular sensing, *Phys. Rev. E* **108**, 014403 (2023).
- [41] R. Bao and S. Liang, Nonlinear response identities and bounds for nonequilibrium steady states, [arXiv:2412.19602](https://arxiv.org/abs/2412.19602).
- [42] E. Kwon, H.-M. Chun, H. Park, and J. S. Lee, Fluctuation-response inequalities for kinetic and entropic perturbations, *Phys. Rev. Lett.* **135**, 097101 (2025).
- [43] R. Bebon and T. Speck, Mutual linearity is a generic property of steady-state Markov networks, *Phys. Rev. Lett.* **136**, 137401 (2026).
- [44] K. Visscher, M. J. Schnitzer, and S. M. Block, Single kinesin molecules studied with a molecular force clamp, *Nature (London)* **400**, 184 (1999).
- [45] We derived this using the edge reciprocity shown later in Eq. (9) (see the Supplemental Material [34]), consistent with the mutual linearity results independently reported by others [43].
- [46] A. C. Barato and U. Seifert, Thermodynamic uncertainty relation for biomolecular processes, *Phys. Rev. Lett.* **114**, 158101 (2015).
- [47] T. R. Gingrich, J. M. Horowitz, N. Perunov, and J. L. England, Dissipation bounds all steady-state current fluctuations, *Phys. Rev. Lett.* **116**, 120601 (2016).
- [48] J. M. Horowitz and T. R. Gingrich, Thermodynamic uncertainty relations constrain non-equilibrium fluctuations, *Nat. Phys.* **16**, 15 (2020).
- [49] H. Kacser and J. A. Burns, The control of flux, *Biochem. Soc. Trans.* **23**, 341 (1995).
- [50] R. Heinrich and T. A. Rapoport, A linear steady-state treatment of enzymatic chains, *Eur. J. Biochem.* **42**, 89 (1974).
- [51] While such localized tuning can be constructed algebraically from the master equation, CFT naturally extracts this protocol from the Jacobian identity.
- [52] While AI-assisted coding tools lower the barrier to deploying query-specific analytical gradients, a unified mathematical structure remains advantageous as it eliminates repetitive derivations and simplifies debugging.
- [53] Y.-J. Yang and H. Qian, Unified formalism for entropy production and fluctuation relations, *Phys. Rev. E* **101**, 022129 (2020).
- [54] H. B. Callen, *Thermodynamics and an Introduction to Thermostatistics*, 2nd ed. (Wiley, New York, 1985).
- [55] Y.-J. Yang, Codes for “Fluctuation-response design rules for nonequilibrium flows”, Zenodo, 2026, <https://doi.org/10.5281/zenodo.18611573>.