

Mutual Linearity Is a Generic Property of Steady-State Markov Networks

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Understanding and predicting how complex systems respond to external perturbations is a central challenge in nonequilibrium statistical physics. Here, we consider continuous-time Markov networks, which we subject to perturbations along a single edge. We find that in steady state the probabilities of any two states are linearly related to one another. We show that this mutual linearity of probabilities extends to a broad class of observables, including currents but also generic counting and state-dependent observables. Moreover, we derive an exact relation between the relative response of any state's probability and the ratio of two steady-state probabilities. Leveraging the Markov chain tree theorem, we further show that probabilities and the considered observables are constrained by the topological and kinetic properties of the network and provide analytical expressions in terms of spanning tree polynomials. Our results are general, holding for arbitrary rate parametrizations and extending far from equilibrium.

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Introduction—Predicting how physical systems respond to external perturbations is a longstanding challenge in physics. For small perturbations, linear response theory provides a direct connection between the basic properties of an unperturbed system, in the form of its transport coefficients, and its response [1–3]. In thermal equilibrium, this response is entirely characterized by equilibrium fluctuations via the well-known fluctuation-dissipation theorem [4]. More recently, the development of stochastic thermodynamics [5–7] has sparked growing interest in understanding the response of nonequilibrium systems that capture the dissipative dynamics of, e.g., chemical reaction networks [8–12] or active matter [13–17]. Numerous generalizations and extensions of the fluctuation-dissipation theorem have since been proposed [18–31].

In parallel, predominantly for continuous-time Markov jump processes, a variety of approaches has been explored to characterize the nonequilibrium response of different observables. Drawing inspiration from thermodynamic uncertainty relations [32–35], the response of steady-state observables [36,37]—and their precision [28,38,39]—is fundamentally constrained by dissipation. Similarly, topological constraints encoded in the incidence matrix provide exact response relations [40] and structural features such as the size of the support of the perturbation [41] delineates the sensitivity of steady-state observables.

A particularly intriguing response property was unveiled by Harunari *et al.* [42] in proving that, upon perturbing a single edge's rates, any two currents are linearly related. This holds arbitrarily far from equilibrium and follows independent of thermodynamic consistency constraints, i.e., local-detailed balance, making it a fundamental property of any irreducible Markov jump process. Further works were devoted to enrich the results of Ref. [42] by assigning response coefficients a clear physical interpretation in form of first-passage times [43] and proving mutual linearity relations for currents to hold more generally in cases where perturbations are supported by multiple edges [44]. In this Letter, we prove an even more fundamental linear relation between any two state-steady probabilities, from which it is straightforward to show that mutual linearity holds for edge currents. We apply our result to a broad class of observables, including state-dependent and generic counting observables. As a consequence, any combination of such observables, e.g., the probability to occupy state n and the traffic through edge $n \leftrightarrow m$, are linearly related, and we provide two different analytical expressions for their respective susceptibilities. Additionally, as a corollary, we find that the relative response of any state in the system is identical and determined by the ratio of only two probabilities: the probabilities of the states connected via the input edge.

Setup and results—We consider continuous-time Markov networks consisting of a discrete set of $|\mathcal{N}|$ vertices (or states) $n \in \mathcal{N}$ that are connected via edges. Transitions between two states n and m occur with transition rates k_{nm} from $n \rightarrow m$. We assume networks to be irreducible, meaning that every state n can be reached from any other state m within the network in finite time; this also guarantees the existence of a unique stationary

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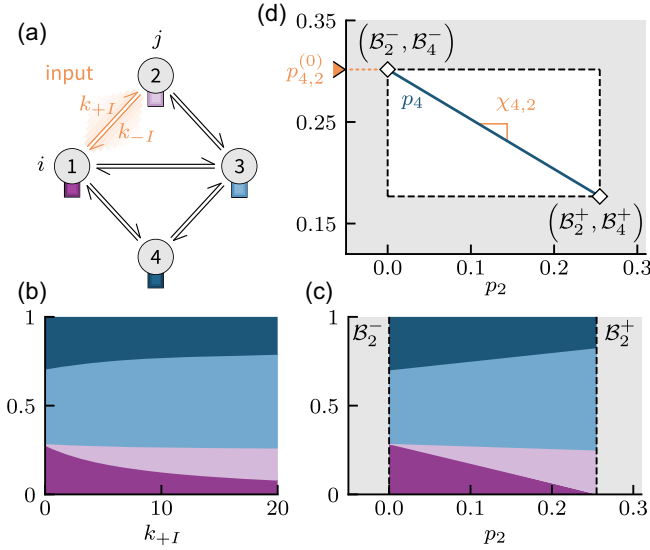


FIG. 1. (a) Markov network consisting of four states. The controlled input edge I (orange) is spanned by states $i = 1$ and $j = 2$. (b) Occupation probabilities as function of rate k_{+I} while k_{-I} is fixed. Probabilities are colored according to the labels in (a). (c) Linear relation [Eq. (2)] between probabilities. All probabilities are linear in the reference probability p_2 . Dashed lines depict the limits of values accessible to p_2 [Eq. (7)]. (d) Probability p_4 over p_2 together with the rectangular phase space region spanned by their respective bounds and markers indicate the corners of the diagonal that contains the possible solutions. The affine coefficient $p_{4,2}^{(0)}$ and susceptibility $\chi_{4,2}$ entering Eq. (2) are indicated in orange.

state [45]. Probability rates and the network topology are encoded in the rate matrix $\mathbf{W}$ with off-diagonal $[\mathbf{W}]_{n,m} = k_{mn}$ and diagonal entries $[\mathbf{W}]_{n,n} = -\sum_{m \neq n} k_{nm}$ such that columns sum to zero to ensure probability conservation. The time evolution of the probability distribution is governed by the master equation $\partial_t \mathbf{p} = \mathbf{W} \mathbf{p}$ and we collect occupation probabilities of the stationary solution ($\partial_t \mathbf{p} = 0$) in the normalized vector $\mathbf{p} = (p_1, p_2, \dots, p_{|\mathcal{N}|})^\top$.

Inspired by recent results [40,42,43], we study the stationary response of Markovian jump processes to changes in the rates $k_{+I} \equiv k_{ij}$ and $k_{-I} \equiv k_{ji}$ of an externally controlled edge $I \equiv i \leftrightarrow j$ [see Fig. 1(a)], henceforth referred to as the input edge. In general, we allow simultaneous variation of both input rates, or each individually, while the remaining network is kept unchanged. As one of the fundamental quantities of a Markov network, we focus our attention on steady-state probabilities and leverage the relation

$$\partial_k \mathbf{p} = -\mathbf{W}_n^{-1} (\partial_k \mathbf{W}_n) \mathbf{p}, \quad (1)$$

which has been derived recently and provides a linear algebra-based method to determine nonequilibrium responses [40]. Here, k denotes an arbitrary rate, or more

generally a rate parameter, and we define $\mathbf{W}_n$ as the rate matrix $\mathbf{W}$ with the n th row replaced by ones [cf. Eq. (A1)]. Unlike the Markov generator matrix, $\mathbf{W}_n$ is invertible for any n [40,42,46] and normalization dictates $\mathbf{W}_n \mathbf{p} = \mathbf{e}_n$, where $\mathbf{e}_n$ is the unit vector with 1 as its n th element. Equation (1) follows from simple differentiation.

Plugging $\mathbf{W}_i$ and $k = k_{\pm I}$ into Eq. (1), we find that the responses of any two states n and $m \in \mathcal{N}$ satisfy $\partial_{k_{\pm I}} p_n / (\partial_{k_{\pm I}} p_m) = \chi_{n,m}$, where $\chi_{n,m}$ is independent of rates $k_{\pm I}$. The probabilities thus satisfy

$$p_n(k_{\pm I}) = p_{n,m}^{(0)} + \chi_{n,m} p_m(k_{\pm I}) \quad (2)$$

for all values of $k_{\pm I}$ associated with the freely chooseable input edge I [47]. This constitutes our first main result. For a detailed proof, see Appendix A. Although probabilities are nonlinear functions of the transition rates [cf. Fig. 1(b)], Eq. (2) states that changing the rates of a single edge triggers a linear response between any two states n and m [cf. Fig. 1(c)], with $\chi_{n,m}$ denoting the probability-probability susceptibility, i.e., the sensitivity of probability p_n to changes in p_m . It is given by the algebraic expression

$$\chi_{n,m} \equiv \frac{[\text{adj}(\mathbf{W}_i)]_{n,j}}{[\text{adj}(\mathbf{W}_i)]_{m,j}}, \quad (3)$$

where $[\text{adj}(\mathbf{M})]_{n,m} \equiv (-1)^{n+m} \det(\mathbf{M}_{\setminus(n,m)})$ denotes elements of the adjugate matrix, or equivalently the transpose of the cofactor matrix, of a square matrix $\mathbf{M}$. The subscript “ $\setminus(n,m)$ ” indicates deletion of the n th row and m th column. Susceptibilities defined through Eq. (3) remain invariant to changes in the input rates since they appear only in the j th row of $\mathbf{W}_i$ [cf. Eq. (A1)]. Furthermore, they are invariant under global rescaling of rates and satisfy the identities

$$\chi_{n,m} = \frac{1}{\chi_{m,n}}, \quad \frac{\chi_{n,m}}{\chi_{n,l}} = \chi_{l,m}, \quad \frac{\chi_{n,m}}{\chi_{l,m}} = \chi_{n,l}. \quad (4)$$

Remarkably, a change of reference state, e.g., $m \rightarrow l$ in Eq. (3), results in a global rescaling of all susceptibilities by the constant factor $1/\chi_{l,m}$. The same holds for changes in the target probability. Thus, the normalized magnitude of susceptibilities is universal within any network. If both states coincide, $\chi_{n,n} = 1$, as expected. At this stage the affine coefficients in Eq. (2) remain undetermined integration constants. We will derive exact expressions for these offsets later.

As a direct corollary of Eqs. (2) and (3), we obtain a relation between the ratio of an arbitrary state’s response to changes in the forward and backward rates along the input edge and the probability of states that span that edge

$$-\frac{\partial_{k_{+I}} p_n}{\partial_{k_{-I}} p_n} = \frac{p_i}{p_j}. \quad (5)$$

For $p_j = 0$ the response $\partial_{k_{+I}} p_n$ vanishes [Eq. (A2)] and taking the ratio is mathematically undefined. From an operational perspective, Eq. (5) allows the direct inference of each state's relative sensitivity from the occupation probabilities of only two states and vice versa. Moreover, if the input edge obeys detailed balance, $p_i k_{+I} = p_j k_{-I}$, Eq. (5) reduces to $-\partial_{k_{+I}} p_n / (\partial_{k_{-I}} p_n) = k_{-I} / k_{+I}$, and links the nonequilibrium responses of all states in the system to the equilibrium thermodynamic potentials encoded in the transition rates of a single edge. Employing the results of Ref. [48], we show in [49] that the response ratio in Eq. (5) can be bounded in terms of pseudoequilibrium quantities that depend on thermodynamic properties only.

Probability bounds—Next we use standard graph theory identities to bound the region of phase space accessible to stationary probabilities when controlling a single edge's transition rates. According to Kirchhoff's Markov chain tree theorem [53–55] the stationary probability of a given state n can be expressed as $p_n = \tau_n / \sum_y \tau_y$. Here, $\tau_n = \sum_\mu w(\mathcal{T}_n^\mu)$ sums over all spanning trees μ , and $w(\mathcal{T}_n^\mu)$ is the product of transition rates along the directed tree $\mathcal{T}_n^\mu$ rooted at n [56]. To isolate the influence of the external control, we introduce the decomposition [42]

$$\tau_n = \tau_{n \setminus i \leftrightarrow j} + k_{+I} \tau_n^{/i \rightarrow j} + k_{-I} \tau_n^{/j \rightarrow i}, \quad (6)$$

where the first term on the right-hand side denotes the sum over the subset of trees that exclude any transitions through edge I . The term $\tau_n^{/i \rightarrow j}$ ($\tau_n^{/j \rightarrow i}$) represents the sum over trees that do contain transition $i \rightarrow j$ ($j \rightarrow i$), while rate k_{+I} (k_{-I}) is factored out of the product. The decomposition Eq. (6) is a linear function of the input rates, while residual polynomials [τ 's on the right-hand-side of Eq. (6)] are independent of $k_{\pm I}$. These polynomials are easily evaluated numerically [49].

Using the Markov chain tree theorem together with Eq. (6), we can formally evaluate the limits $\lim_{k_{\pm I} \rightarrow \infty} p_n$ to obtain the (asymptotically exact) bounds,

$$\mathcal{B}_n^+ \equiv \frac{\tau_n^{/i \rightarrow j}}{\sum_l \tau_l^{/i \rightarrow j}}, \quad \mathcal{B}_n^- \equiv \frac{\tau_n^{/j \rightarrow i}}{\sum_l \tau_l^{/j \rightarrow i}}, \quad (7)$$

that limit the achievable values of p_n . Because of the nonmonotonic response of probabilities with respect to input rates [cf. Fig. 1(b)], determining which of the bounds from Eq. (7) corresponds to the upper [$\max(\mathcal{B}_n^+, \mathcal{B}_n^-)$] and lower boundary [$\min(\mathcal{B}_n^+, \mathcal{B}_n^-)$] of solution space must be done *a posteriori* and separately for each state n [57].

For any pair of states n and m , the bounds [Eq. (7)] span a (rectangular) region in the (p_n, p_m) plane that contains all steady-state solutions achievable through changes in input

edge I . Invoking the mutual linearity condition from Eq. (2), we know *a priori* that all possible solution pairs (p_n, p_m) condense onto a straight line and thus all permitted solutions lie on the diagonal spanned between $(\mathcal{B}_n^-, \mathcal{B}_m^-)$ and $(\mathcal{B}_n^+, \mathcal{B}_m^+)$, the corners of the rectangular phase space region [cf. Fig. 1(d)]. The offset and slope of the diagonal provide explicit expressions for the affine coefficient and susceptibility of Eq. (2),

$$p_{n,m}^{(0)} = \frac{\mathcal{B}_n^- \mathcal{B}_m^+ - \mathcal{B}_m^- \mathcal{B}_n^+}{\mathcal{B}_m^+ - \mathcal{B}_m^-}, \quad \chi_{n,m} = \frac{\mathcal{B}_n^+ - \mathcal{B}_n^-}{\mathcal{B}_m^+ - \mathcal{B}_m^-}. \quad (8)$$

The latter presents an alternative to the linear algebra-based susceptibilities from Eq. (3) in terms of spanning tree ensembles. Note that $\mathcal{B}_i^+ = 0$ since transitions $i \rightarrow j$ are prohibited for any tree rooted in i and hence $\tau_i^{/i \rightarrow j} = 0$; the same holds for $\mathcal{B}_j^-$. As a result, the offset in Eq. (8) simplifies to, e.g., $p_{n,j}^{(0)} = \mathcal{B}_n^-$ [cf. Fig. 1].

In Appendix B we provide additional bounds for the case of single rate control or unidirectional input edges. The corresponding susceptibilities and offsets follow in analogy to Eq. (8).

General observables—We now shift our attention to a broad class of observables that we express as

$$\mathcal{O}_A \equiv \alpha \sum_{m \in A} c_m p_m + \beta \sum_{l,m \in A \setminus \{I\}} d_{ml} k_{ml} p_m, \quad (9)$$

with constant coefficients c_m and d_{mn} . The sums run over all states and transitions contained in $A \subseteq \mathcal{N}$, excluding I . For $\beta = 0$, Eq. (9) describes a state-dependent observable that weighs state occupation with weights c_m . Conversely, $\alpha = 0$ defines a counting observable that is either trafficlike or currentlike depending on the signs of increments d_{ml} . In case $d_{ml} = d_{lm}$, Eq. (9) is time-symmetric and, for unit coefficients, reduces to the dynamical activity (rate) [58–61] (closely related to frenesy [62]) of all edges supported by the states of $A \setminus \{I\}$. Similarly, for $d_{ml} = -d_{lm} = 1$, Eq. (9) measures directed flows and reduces to the edge current j_{ml} if A encompasses only states m and l .

As a straightforward generalization of Eq. (2), we find that all observables of the form in Eq. (9) are likewise linear to each other and satisfy

$$\mathcal{O}_A = \left(\mathcal{O}_{A,n}^{(0)} - \frac{\mathcal{X}_{A,n}}{\mathcal{X}_{B,n}} \mathcal{O}_{B,n}^{(0)} \right) + \frac{\mathcal{X}_{A,n}}{\mathcal{X}_{B,n}} \mathcal{O}_B, \quad (10)$$

with

$$\begin{bmatrix} \mathcal{O}_{A,n}^{(0)} \\ \mathcal{X}_{A,n} \\ \mathcal{B}_{\mathcal{O}_A}^\pm \end{bmatrix} \equiv \alpha \sum_{m \in A} c_m \begin{bmatrix} p_{m,n}^{(0)} \\ \chi_{m,n} \\ \mathcal{B}_n^\pm \end{bmatrix} + \beta \sum_{l,m \in A \setminus \{I\}} d_{ml} k_{ml} \begin{bmatrix} p_{m,n}^{(0)} \\ \chi_{m,n} \\ \mathcal{B}_n^\pm \end{bmatrix}. \quad (11)$$

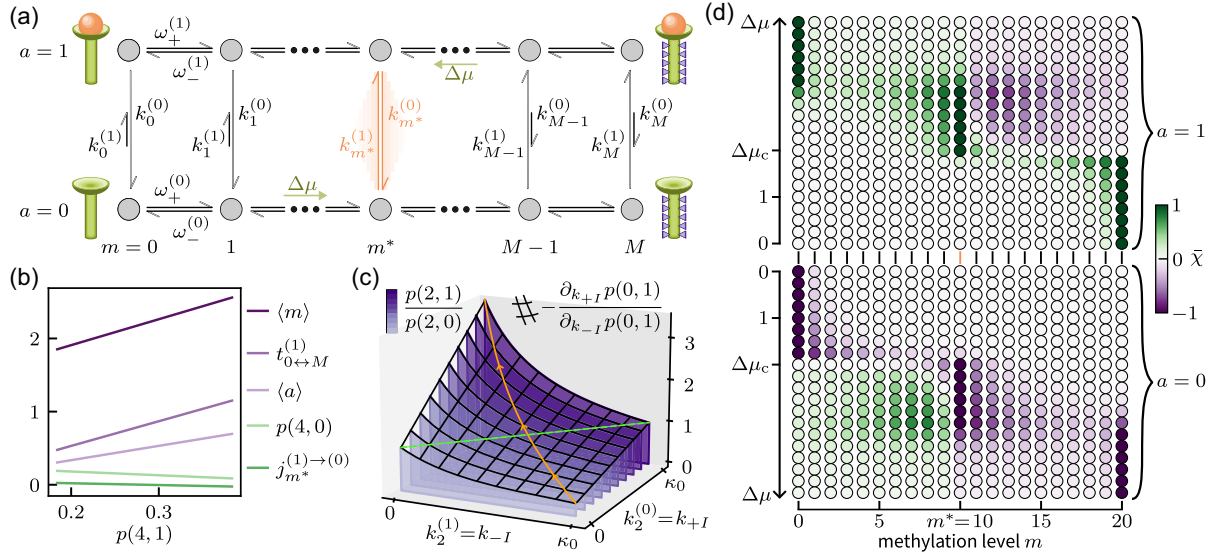


FIG. 2. (a) Adaptation model for a chemoreceptor with a total of $|\mathcal{N}| = 2(M+1)$ states comprising the activity state $a \in \{0, 1\}$ and the methylation level $m \in \{0, \dots, M\}$ (purple triangles). Occupation probabilities are denoted as $p(m, a)$. (b) Mutual linearity between the average methylation $\langle m \rangle$ [Eq. (D1)], average activity $\langle a \rangle$ [Eq. (D2)], mesoscopic edge traffic $t_{0 \leftrightarrow M}^{(1)}$ [Eq. (D3)], current through the input edge $j_{m^*}^{(1) \rightarrow (0)}$ [Eq. (D4)], and probabilities $p(4, 0)$ and $p(4, 1)$. (c) Comparison between the ratio of probabilities connected by the input edge $p(2, 1)/p(2, 0)$ (colors) and the relative response $-\partial_{k_{+I}} p(0, 1)/[\partial_{k_{-I}} p(0, 1)]$ (wireframe). For the dashed green line, edge I obeys detailed balance and the probability and response ratios equal k_{-I}/k_{+I} . The solid orange line indicates the protocol we adopt for input rates in panels (b) and (d). In panels (b) and (c) we consider a sensory network with $M = 4$ methylation levels, $\Delta\mu = 1.3$, and the input edge connects activity states at methylation level $m^* = 2$. (d) Normalized susceptibilities of the adaptation model with $M = 20$ methylation levels as we vary the driving strength $\Delta\mu$. Each circle corresponds to a state of the active $a = 1$ (top) or passive $a = 0$ branch (bottom) and is colored according to its susceptibility obtained from normalizing the results of Eq. (3), with reference probability $p(10, 1)$. The input edge is located at $m^* = 10$ and indicated in orange.

The last line defines the generalization of the bounds from Eq. (7), which can be used to determine mesoscopic susceptibilities $\mathcal{X}_{A,n}$ and $\mathcal{O}_{A,n}^{(0)}$ through Eq. (8). In case $\mathcal{O}_B = 0$ for all $k_{\pm I}$, i.e., $\mathcal{B}_{\mathcal{O}_B}^{\pm} = 0$, Eq. (10) no longer holds since susceptibilities are mathematically undefined [63].

For single rate perturbations and time-asymmetric counting observables on edge I , i.e., $d_{ij} = -d_{ji}$, the second summation in Eq. (9) can be extended to include edge I , as the explicit dependence on the rates $k_{\pm I}$ cancels [49]. This allows us to immediately recover the key results of Refs. [42,43], where the linearity of currents was derived by other means. Our findings augment these works by proving that mutual linearity is a fundamental property of steady-state probabilities [Eq. (2)], from which it naturally extends to a broad class of observables [see Eqs. (9) and (10)], including currents.

Sensory adaptation—To illustrate the results of this Letter, we adopt an idealized biophysical model of sensory adaptation that is motivated by the chemotaxis pathway in *E. coli* [64–66]. The process is described through the Markovian network shown in Fig. 2(a) and captures the mesoscopic dynamics of the binary activity state $a \in \{0, 1\}$ and the degree of methylation m of a concentration sensing chemoreceptor [67,68]. We assume that the transition rates between the activity states at $m = m^*$ are sensitive to an

external signal and we treat it as input edge in the following. For chemotaxis adaptation, this signal relates to the (logarithmic) concentration of chemoattractants [69–71]. The remaining rates between activity states are left constant and biased according to the arrows in Fig. 2(a). For given activity, transitions are independent of the degree of methylation and the system relaxes into the energetically favored state of low (high) methylation for the inactive (active) branch, unless the chemical energy input $\Delta\mu$ is sufficiently strong to drive transitions uphill the free energy landscape [cf. Fig. 4 in Appendix D]. Further details are provided in Supplemental Material [49].

In Figs. 2(b) and 2(c), we illustrate our main results from Eqs. (2), (10), and (5) for an adaptation ladder containing $M = 4$ methylation levels and an input edge connecting activity states at $m^* = 2$. Figure 2(b) depicts the linear relationship between various state observables ($\langle a \rangle$, $\langle m \rangle$), counting observables ($j_{m^*}^{(1) \rightarrow (0)}$, $t_{0 \leftrightarrow M}^{(1)}$) and probabilities $p(m, a)$. Susceptibilities and offsets follow from Eqs. (3), (8), and (11), respectively. For the relative response of, e.g., probability $p(0, 1)$, we confirm Eq. (5) in Fig. 2(c), which thus enables the inference of the network sensitivity to changes in rates $k_{\pm I}$ through limited knowledge in form of the two probabilities $p(2, \{0, 1\})$. Specifically, for $k_{+I} > k_{-I}$, probabilities are more responsive to changes in

k_{+I} and vice versa. For $k_{+I} = k_{-I}$ probabilities are equally responsive, which, owing to the symmetric choice of transition timescales along activity axes, coincides with a vanishing current through the controlled edge.

Depending on the chemical energy input $\Delta\mu$ the system operates in either of two different modes: sensitive or adaptive [72]. For $\Delta\mu < \Delta\mu_c$ the system's activity is highly sensitive to alterations in the external signal, biasing relaxation into either the active $p(M, 1)$ or inactive $p(0, 0)$ state. Conversely, beyond a critical driving strength $\Delta\mu > \Delta\mu_c$ the system compensates changes in the external signal by adapting its internal methylation state and ensures a robust activity output $\langle a \rangle$ by stabilizing dissipative cycles around the adapted level of methylation (here, m^* for $S = 0$) [49]. Indeed, Ref. [73] shows that the onset of adaptation for such models can be described as a (continuous) nonequilibrium phase transition with $\Delta\mu$ acting as control parameter.

Employing Eq. (2) to an extended system with $M = 20$ levels, we find in Fig. 2(d) that the adaptation onset coincides with a pronounced change in the susceptibilities. Notably, the depicted normalized susceptibilities are, apart from their sign, independent of the chosen reference state [cf. Eq. (4)]. The susceptibility patterns are most easily understood by considering how probability is redistributed within the system [cf. Fig. 4]: for $\Delta\mu < \Delta\mu_c$, probability is concentrated in the energetically favored states $p(0, 0)$ and $p(M, 1)$. Because these states are highly populated, even small perturbations in the input produce comparatively large changes in their stationary weights, rendering them most susceptible. Conversely, if the critical driving strength is exceeded, input-induced changes predominantly redistribute probability among the states that participate in dissipatively stabilized cycles, causing susceptibilities to localize around the adapted methylation level m^* . The number of methylation levels traversed by these cycles increases with $\Delta\mu$ until probability is collected in $p(M, 0)$ and $p(0, 1)$ through persistent edge currents.

Discussion—In this Letter, we prove that any two steady-state probabilities of continuous-time Markov networks are linearly related [Eq. (2)]. We show that this linearity relation translates to a broad class of observables [Eq. (10)], including state-dependent and counting observables, which allows us to recover and considerably extend earlier results on the mutual linearity of steady-state currents reported in Refs. [42,43].

All coefficients entering our main results in Eqs. (2) and (10) are empirically accessible through measuring two combinations of probabilities (e.g., through fluorescence techniques [74–76], force [77,78], plasmon ruler spectroscopy [79,80], etc.) or observables under different external input. Hence, additional measurements have predictive power and comparing susceptibilities offers a robust method for proof testing viable candidate models [42]. Moreover, once coefficients of affine transformations are

established (e.g., between a current and the total dynamical activity), measurement of either of the two quantities allows simultaneous inference of the other. We present two methods to numerically evaluate susceptibilities: (i) through the linear-algebra-based expression in Eq. (3), or (ii) by evaluating tree polynomials that enter the bounds in Eq. (7) [Eq. (11)]. These bounds additionally offer analytical expressions for the affine coefficients entering Eqs. (2) and (10) and delineate the space of possible solutions.

Our results are general, hold arbitrarily far from thermal equilibrium, and make no assumptions about the parametrization of transition rates. If instead one assumes an explicit parametrization in the form of Arrhenius- [81] or Eyring-like [82] rates, we prove a set of response relations for observables $\mathcal{O}_A$ [Eq. (9)] in Ref. [49] that encompass previous identities [46] upon choosing the corresponding observables, but also hold more broadly for nonlocal responses. Furthermore, edge transitions are not required to be bidirectional (see Appendix C) and transitions over an edge can occur through multiple reaction channels.

Throughout, we focused on continuous-time Markov networks and leverage the properties of the rate matrix $\mathbf{W}$ to derive Eq. (2) and corollary results. Since similar type of matrices are encountered in various other contexts, e.g., for the voter model [83–86], it would be interesting to explore the ramifications of our work also in these systems.

Note added—After acceptance, we became aware of independent work [87] deriving a result closely related to Eq. (2).

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Data availability—The data that support the findings of this article are openly available [88].

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End Matter

Appendix A: Proof of linearity of steady-state probabilities—We use Eq. (1) to calculate the response of steady-state probabilities subjected to perturbations in the rates $k_{\pm I}$. We consider the matrix

$$\mathbf{W}_i = \begin{pmatrix} & i & j & \\ \ddots & & & \\ & 1 & 1 & \\ k_{+I} & -k_{-I} & \dots & \\ & & \ddots & \end{pmatrix} \begin{matrix} i \\ j \end{matrix} \quad (\text{A1})$$

in which the appearance of input rates $k_{\pm I}$ is reduced to only two entries: (i, j) and the diagonal element (j, j) . We find

$$\begin{aligned} \partial_{k_{+I}} p_n &= -[\mathbf{W}_i^{-1}]_{n,j} p_i = -\frac{[\text{adj}(\mathbf{W}_i)]_{n,j}}{\det(\mathbf{W}_i)} p_i \\ \partial_{k_{-I}} p_n &= [\mathbf{W}_i^{-1}]_{n,j} p_j = \frac{[\text{adj}(\mathbf{W}_i)]_{n,j}}{\det(\mathbf{W}_i)} p_j \end{aligned} \quad (\text{A2})$$

for an arbitrary vertex n . The second equalities are obtained by exploiting the relation between adjugate matrix $\text{adj}(\mathbf{W}_i)$, with $[\text{adj}(\mathbf{W}_i)]_{n,m} \equiv (-1)^{n+m} \det(\mathbf{W}_{i \setminus (m,n)})$ —this is equivalent to the transpose of the cofactor matrix of $\mathbf{W}_i$ —and inverse of $\mathbf{W}_i$,

$$\text{adj}(\mathbf{W}_i) = \mathbf{W}_i^{-1} \det(\mathbf{W}_i). \quad (\text{A3})$$

As our main result, we find from Eqs. (A2) and (A3)

$$\frac{\partial_{k_{\pm I}} p_n}{\partial_{k_{\pm I}} p_m} = \frac{[\text{adj}(\mathbf{W}_i)]_{n,j}}{[\text{adj}(\mathbf{W}_i)]_{m,j}} \equiv \chi_{n,m}. \quad (\text{A4})$$

The mutual linearity relation in Eq. (2) then follows immediately. The relation holds except if $p_m = 0$ for all $k_{\pm I}$, which is generally impossible for irreducible graphs unless transition rates are infinitely large.

Appendix B: Probability bounds for unidirectional control—While the bounds in Eq. (7) also hold if only one of the input rates is controlled or if the edge is totally irreversible, the bound corresponding to the fixed (or zero) rate overestimates the range of accessible values. Instead, $\lim_{k_{\pm I} \rightarrow 0} p_n$ results in the bounds

$$\mathcal{U}_n^+ \equiv \frac{\tau_{n \setminus i \rightarrow j}}{\sum_l \tau_{l \setminus i \rightarrow j}}, \quad \mathcal{U}_n^- \equiv \frac{\tau_{n \setminus j \rightarrow i}}{\sum_l \tau_{l \setminus j \rightarrow i}}, \quad (\text{B1})$$

which limit all possible solutions. Note that writing $\tau_{n \setminus i \rightarrow j} = \tau_{n \setminus i \leftrightarrow j} + k_{-I} \tau_n^{j \rightarrow i}$, and analog for $\tau_{n \setminus j \rightarrow i}$, the bounds are independent of the controlled rate. Analytical expressions for the affine coefficients and susceptibilities follow from Eq. (8) upon replacing $\mathcal{B}_{\{n,m\}}^{\pm} \rightarrow \mathcal{U}_{\{n,m\}}^{\mp}$ for the respective cases.

Appendix C: Calmodulin folding—For a second concrete illustration, we consider an experimentally inferred folding network of single calmodulin proteins [77], which we augment by a unidirectional irreversible transition that stochastically “resets” [89–92] the protein from the intermediate state “3” to the unfolded state “1” with rate $k_{+I} \equiv r$ [Fig. 3(a)]. This unidirectional transition is subjected to external control while the remaining rates are fixed and satisfy detailed balance [49,93], i.e., for $r = 0$ the system is in thermal equilibrium. Importantly, the irreducibility assumption entering Eq. (2) is satisfied by networks containing unidirectional transitions, provided absorbing states are absent and all bridges—edges that connect otherwise isolated subsets of states—are microscopically reversible.

While the probabilities to observe different protein configurations are nonlinear functions of r , they are linearly related to each other [Eq. (2)]. For instance, all probabilities vary linearly with p_1 —the probability of the unfolded state—as depicted in Fig. 3(b). However, although we allow $r \geq 0$ to take arbitrarily large values, the redistribution of probability among states is intrinsically limited by the topology and kinetic properties of the network, which restricts viable solutions to the values bounded by $\mathcal{B}_n^+$ [Eq. (7)] and $\mathcal{U}_n^+$ [Eq. (B1)]. The latter replaces $\mathcal{B}_n^-$ for

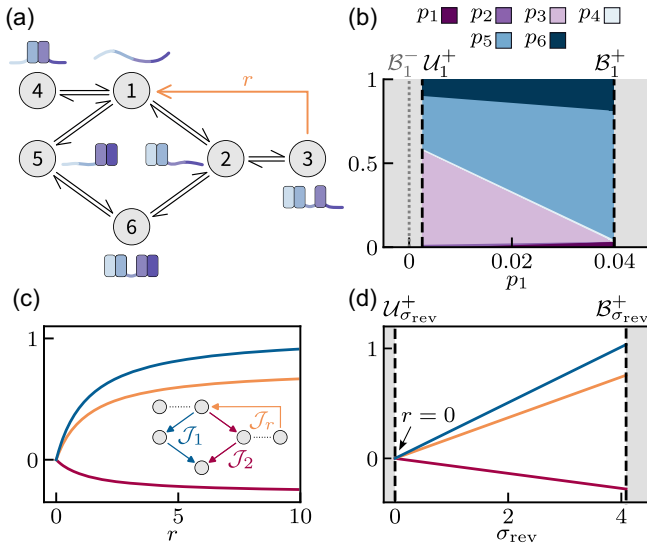


FIG. 3. (a) Calmodulin folding network [77] with an added unidirectional resetting transition with rate r (orange) from an intermediate “3” to the unfolded state “1.” The unidirectional rate is subject to external control. (b) Linear relation between steady-state probabilities and p_1 . The black dashed lines and gray shaded areas indicate the bounds on p_1 given by Eqs. (7) and (B1) respectively. The gray dotted line shows the bound B_1^- [Eq. (7)]. (c) Currents through the two different folding pathways $\mathcal{J}_1 \equiv j_{15} + j_{56}$ and $\mathcal{J}_2 \equiv j_{12} + j_{26}$, as well as the resetting flux $\mathcal{J}_r \equiv p_3 r$ (see inset) over the resetting rate r . (d) The same observables as in (c) plotted over the entropy production rate of all microscopically reversible transitions $\sigma_{\text{rev}} \equiv \sum_{n < m \in \mathcal{N} \setminus \{I\}} j_{nm} \ln(k_{nm}/k_{mn})$.

the unidirectional input edge considered here (see Appendix B).

Along similar lines, observables expressed through Eq. (9) depend nontrivially on the controlled rate r [Fig. 3(c)]. Among themselves, however, any two observables are linearly related according to Eq. (10). In Fig. 3(d) we illustrate the linear relationship between the mesoscopic currents $\mathcal{J}_{\{1,2\}}$ through different folding pathways, the resetting flux $\mathcal{J}_r$ (see inset), and the entropy production rate of all microscopically reversible transitions σ_{rev} [94,95]. The associated affine coefficients, susceptibilities, and bounds follow straightforwardly from Eq. (11).

Appendix D: Sensory adaptation—To illustrate the broad range of applicability of the linearity relations in Eqs. (2) and (10), we examine various observables in Fig. 2(b). As state observables we consider the average methylation level, defined as

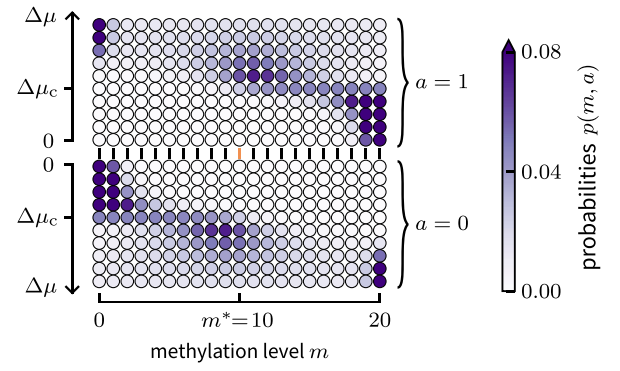


FIG. 4. Steady-state probabilities of a chemotaxis ladder with $M = 20$ methylation levels for various driving strengths $\Delta\mu$ (in steps of 0.5). Each circle corresponds to a state of the active $a = 1$ (top) and passive $a = 0$ (bottom) branch. Colors indicate the occupation probabilities, where we cap the color bar at a value of 0.08 to improve readability. The input edge located at $m^* = 10$ is highlighted in orange. Here, we use $S = 0$, such that cycles are centered around m^* [49].

$$\langle m \rangle \equiv \sum_{m=0}^M m[p(m, 0) + p(m, 1)], \quad (\text{D1})$$

and the average output activity

$$\langle a \rangle \equiv \sum_{m=0}^M p(m, 1), \quad (\text{D2})$$

which characterizes the fraction of time the receptor spends in its active, $a = 1$, state. As counting observables we consider the mesoscopic traffic along the activity axis $a = 1$,

$$t_{0 \leftrightarrow M}^{(1)} \equiv \sum_{m=0}^{M-1} [p(m, 1)\omega_+^{(0)} + p(m+1, 1)\omega_-^{(0)}], \quad (\text{D3})$$

and the current through the input edge at $m^* = 2$,

$$j_{m^*}^{(1) \rightarrow (0)} \equiv p(m^*, 1)k_{m^*}^{(0)} - p(m^*, 0)k_{m^*}^{(1)}. \quad (\text{D4})$$

For a proof that the input current indeed satisfies a linearity relation, although it appears to depend on $k_{\pm I}$ explicitly, see Supplemental Material [49].

To corroborate the discussion of the sensory adaptation model, Fig. 4 depicts the steady-state probabilities of a network with $M = 20$ methylation levels. The same model is considered in Fig. 2(d).