Circuit Reduction of Heterogeneous Nonequilibrium Systems

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Predicting the behavior of heterogeneous nonequilibrium systems is currently analytically intractable. Consequently, complex biological systems have resisted unifying principles. Here, I introduce a mapping from dynamical systems to battery-resistor circuits. I show that in these transformed variables (i) arbitrary numbers of heterogeneous dynamical transitions can be reduced to a Thevenin equivalent resistor which is invariant to driving from equilibrium, (ii) resistors (together with the external driving sources) are sufficient to describe system behavior, and (iii) the resistor's directional symmetry leads to universal theorems of nonequilibrium behavior. This mapping is used to derive two general steady-state relations. First, for any cyclic process, the maximum amplification of any state is tightly bounded by the total dissipation of all states; experimental data are used to show that the master signal protein Ras achieves this bound. Second, for any process, the response of any reaction due to driving any other reaction is identical to the reciprocal response rescaled by the ratio of the corresponding Thevenin resistors. This result generalizes Onsager's reciprocal relation to the strongly driven regime and makes a testable prediction about how systems should be designed or evolved to maximize response. These analytic results represent a new perspective applicable to biological complexity and suggest that this mapping provides the natural variables to study heterogeneous nonequilibrium systems.

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For an equilibrium system, which reaches the detailed-balance condition that the rate of all time-averaged reactions are equal to that of their reverse reactions, the Boltzmann distribution directly gives the relative probability of any state irrespective of the interaction complexity and heterogeneity [1]:

$$P_i^* e^{\beta G_i} = P_j^* e^{\beta G_j}, \tag{1}$$

where G_i is the free energy of state i and $\beta = (k_B T)^{-1}$ is the reciprocal of Boltzmann's constant times the temperature. Equilibrium probabilities in this work are denoted with a "*" superscript. Most systems in nature operate far from equilibrium. Examples include molecular and cellular biology, cognition, evolution, and socioeconomics [2–6]. The energy driving these systems is necessary to enable features—such as irreversible or sharp decision making—that are impossible at equilibrium [7]. Such systems do not obey Eq. (1).

The most direct general approach to compute nonequilibrium steady-state probabilities is to solve the master equations describing the transition rates within the network of system states. If the network is homogeneous, corresponding to a periodic graph structure parametrized by a small number of repeating rate constants, the master equations can sometimes be analytically solved using the method of generating functions [8,9]. For heterogeneous systems with irregular graph structure or nonrepeating rate constants, the symbolic solution becomes intractable if the system has more than a few states. For example, the graph theoretic approach of Hill and Schnakenberg, which follows from the matrix tree theorem [10], leads to representations whose complexity grows (super)exponentially with the number of states [11–13]. This drawback thus limits the ability to interpret, generalize, or simplify the dynamical complexity within the network of states. A parallel approach is to relate trajectory probabilities to dissipation, which has led to fundamental equalities [14–17] and inequalities [18,19] out of equilibrium. Near equilibrium, this approach can recover useful relations between measurable quantities such as the celebrated linear-response Onsager reciprocal relation connecting near-equilibrium transport coefficients [20]. However, far from equilibrium, this approach generally does not relate observables to the system parameters. Therefore, unifying organizational principles of heterogeneous nonequilibrium systems are lacking. In particular, the complexity of living systems is still largely regarded as irreducible and case specific.

Here, I show that the master equations describing any dynamical system can be mapped to a probability flow circuit. In such a circuit, net probability flows in the directions that decrease a state variable: the probability potential. There are only three types of circuit elements in this mapping: batteries (energy sources), grounds (mass sources), and resistors (passive dissipative processes). With

this mapping, I derive a probability flux equation (PFE). The resistors in the PFE are symmetric with respect to the net direction of probability flow and obey Ohm's law. The PFE is "path local" because it relates the currents along any trajectory to the probabilities of the initial and final states of the trajectory. The PFE is valid for systems driven arbitrarily far from equilibrium, including those that have not reached steady state. For the "equipotential" special case for which there is no net current (i.e., detailed balance), the path-local PFE reduces to the "state-local" Boltzmann distribution as a special case.

I use the PFE to derive two general relations for nonequilibrium steady states. (1) Resistors in a probability circuit can be merged into an equivalent resistance to reduce complex systems to their irreducible modular representations; for arbitrary cyclic systems, this property is used to prove that the total dissipation tightly bounds the amplification of any signal, no matter how weak. (2) The mapping allows general theorems from electronic circuit theory to be brought to bear on nonequilibrium steady states, from which they take on new meaning. I show that, regardless of system details, the response of one process due to driving another process obeys a simple reciprocal relation that is invariant to magnitude of driving, a generalization of Onsager's reciprocal relation arbitrarily far from equilibrium.

Consider first a discrete-state system at equilibrium. Such a system is completely characterized by forward rate constants between adjacent states k_{mn} and their free energies G_m; the reverse rate constants k_{nm} are then uniquely determined by Eq. (1). A driven system can be defined relative to such an equilibrium reference system: the rate constants in the driven system are equal to those of the reference equilibrium system plus nonequilibrium rate constants, $k_{mn} + \alpha_{mn}$. For example, in the context of biochemical reactions coupled to hydrolysis of adenosine triphosphate (ATP) into adenosine diphosphate (ADP) plus phosphate, α_{mn} corresponds to the excess rate constant of binding ATP due to maintaining the ATP concentration above its equilibrium concentration; the rate constants of the transitions that are not explicitly dependent on ATP concentration are not affected. The net probability flux, denoted by the current I_{mn}, from state m to n is $I_{mn} = P_m(k_{mn} + \alpha_{mn}) - P_n k_{nm}$. Henceforth, the terms "flux" and "current" will be used interchangeably. Define the probability "potential" that drives such a flux (Fig. 1):

$$V_m \equiv P_m e^{\beta G_m}. \tag{2}$$

In this work, G_m always denotes the reference free energy of state m in the absence of driving, whereas P_m always denotes the nonequilibrium probability of state m due to driving. The additive gauge freedom of G_m leads to multiplicative gauge freedom of V_m, which sets it apart from a canonical thermodynamic potential. If the multiplicative constant is chosen to be the equilibrium partition

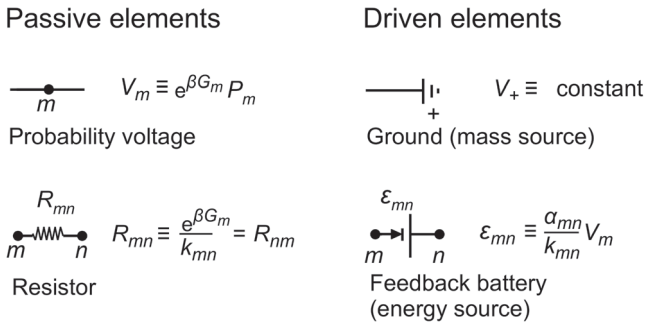

FIG. 1. Mathematical mapping between nonequilibrium systems and probability circuits. The microscopic transitions in state space correspond to elementary circuit elements.

function, V_m is the probability of state m divided by its equilibrium probability. Differences in the V_m drive probability fluxes. If there are source or sink boundary states whose probability (i.e., potential) remains unchanged by probability flux, such states correspond to "grounds." In molecular biology, grounds may correspond to birth or death processes such as protein translation or degradation. With birth or death processes, P_m should be interpreted as the relative occupancy of state m. The occupancy of a ground state can be considered to be infinite, with a reference free energy of negative infinity such that the potential remains fixed. Although not considered further in this work, systems coupled to multiple ground potentials can experience net probability flux. The net probability flux, also called the current I, can be related to the potential V by defining the "resistance" R_{mn} between states m and n (Fig. 1):

$$R_{mn} \equiv \frac{e^{\beta G_m}}{k_{mn}} = R_{nm}. \tag{3}$$

Note that the second equality in Eq. (3) follows because the equilibrium forward flux is equal to the backward flux: the resistance is directionally symmetric, just like the behavior of standard resistors in electronic circuits. Finally, define the "battery" driving transitions from m to n (Fig. 1):

$$\mathcal{E}_{mn} \equiv \frac{\alpha_{mn}}{k_{mn}} e^{\beta G_m} P_m, \tag{4}$$

which is zero when the transition between m and n is not directly driven. $\mathcal{E}_{mn}$ is proportional to the potential at m as defined by Eq. (2); this feedback character differentiates linear versus nonlinear response near and far from equilibrium, respectively.

Equations (2)–(4) define a mapping (see Fig. 1), from which we derive a probability flux equation for any trajectory connecting any pair of states i and j [see Fig. 2(a) and Supplemental Material [21]]:

$$V_j - V_i = \sum_{m=i}^{n=j} (\mathcal{E}_{mn} - R_{mn} I_{mn}), \tag{5}$$

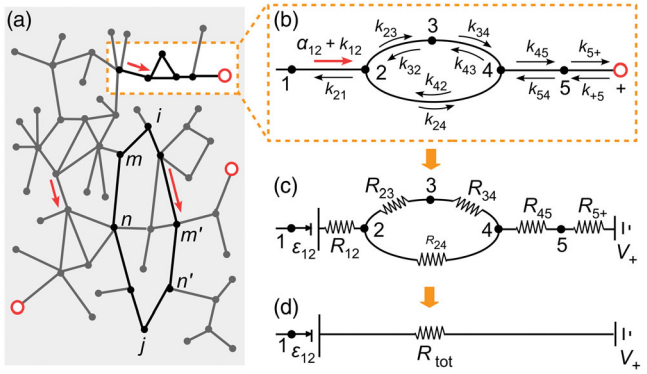

FIG. 2. Top-down simplification of heterogeneous systems. All of the transitions between states of a system (a) are described by forward and reverse rate constants. At equilibrium, all net fluxes equal zero. Injections of matter (red circles) or energy (red arrows), respectively, drive the system out of equilibrium (a),(b), and are governed by Eq. (5) along any trajectory between two nodes (for example, the probability potential difference between i and j can be obtained by taking the PFE over the path containing m,n or the path containg m',n'). The passive resistors can be simplified in a top-down manner using circuit modularization rules (c),(d).

where the sequence of m, n defines the trajectory; note that resistors in the PFE obey Ohm's law.

Equation (5) applies to systems driven far from equilibrium, and holds for all times, not just at steady state. This may give insightful bounds on time-dependent fluxes if time-dependent probabilities can be measured for a few states. At steady state, the PFE is sufficient to solve for currents and probabilities as a function of the elementary parameters, for example, by decomposing into mesh currents; this sets it apart from previous analogies made between dynamical systems and circuits [13,22,23]. For the special equilibrium case, $\alpha_{mn}=0$ for all m and n, all currents are zero, and all states are equipotential, then the PFE [Eq. (5)] simplifies to the Boltzmann distribution Eq. (1). Note that for molecular systems coupled to a temperature bath, the driven transitions (batteries) are clearly identified by the sources of external energy. For abstract master equations parametrized by arbitrary rate constants, there is freedom in defining the reference detailed-balance system, which then uniquely determines the driven transitions; any such choice of circuit variables will satisfy the PFE.

As in electronic circuits, the resistors in a probability circuit can be systematically combined using the rules for combining resistors in parallel or in series, or the star-mesh transform [24]. Using these rules, a complex system can be simplified to a minimal set of Thevenin equivalent resistors which are explicit functions of the microscopic equilibrium parameters [Figs. 2(b)–2(d)]. The reducibility of any system is therefore dictated by the number and placement of driven transitions within the state space. Seemingly different or unrelated dynamical systems may reduce to the same equivalent circuit.

Amplification limit of cyclic processes.—Many molecular machines, such as enzymes and signaling molecules [Fig. 3(a)] belong to the cyclic class of systems whose state space consists of N states arranged in a loop driven by an energy consuming step, which is defined to be from state 1 to 2 without loss of generality [Fig. 3(b)]. The steady-state current for cyclic Markov systems has been solved [25], and the frequency of forward versus backward cycle traversals has been related to the driving force [26]. However, how the probabilities (e.g., signaling amplitude) deviate from equilibrium as a function of driving remains unexplored. When mapped to a probability flux circuit, sequential undriven steps along the loop correspond to resistors in series. The total resistance of any portion of the loop from state i to j is the sum of the individual resistances in the portion: $R_{i;j}\equiv\sum_{m=i}^{j}R_{mm+1}$. The total resistance of the loop is $R_{\mathrm{tot}}\equiv R_{1;N}$ ($N+1=1$ due to periodicity). Solving Eq. (5) yields the probabilities for any cyclic system:

$$P_i=P_i^*\left(\frac{R_{\mathrm{tot}}+(1-\delta_{i1})\frac{\alpha}{k_{12}}R_{i;N}}{R_{\mathrm{tot}}+\frac{\alpha}{k_{12}}\sum_{j=2}^{N}R_{j;N}P_j^*}\right), \tag{6}$$

where P_i^* is the equilibrium probability of state i and δ_{ij} is the Kronecker delta. Amplifying intrinsically low probability states is a major mechanism of cellular information processing [27,28]. The ratio in Eq. (6) is the amplification of the equilibrium probability, which can be selectively tuned by changing the resistors (e.g., lowering energy barriers via catalysts), a feature unavailable to equilibrium systems. From Eq. (6) we establish a simple tight upper bound on the attainable amplification of state i when driving the transition between state 1 and 2 (see Supplemental Material [21]):

$$\frac{P_i}{P_i^*}<\left(\sum_{j=2}^{i}P_j^*\right)^{-1}. \tag{7}$$

Therefore, the extent to which a target state can be amplified by driving a reaction is limited by the equilibrium-probability-weighted distance between the target state and the driven reaction. Until this limit is reached, Eq. (6) also sets the minimal energy cost as a function of amplification:

$$\left|\ln\left(\frac{P_i}{P_i^*}\right)\right|<\frac{Q}{k_BT}. \tag{8}$$

Equation (8) is a tight bound, in which Q is the energy dissipated per net cycle of the entire system, obtained from calculating the rate of entropy production (see Supplemental Material [21]). *No* state of any cyclic process can be amplified or suppressed by a factor more than the exponential of the total dissipation per cycle. This result

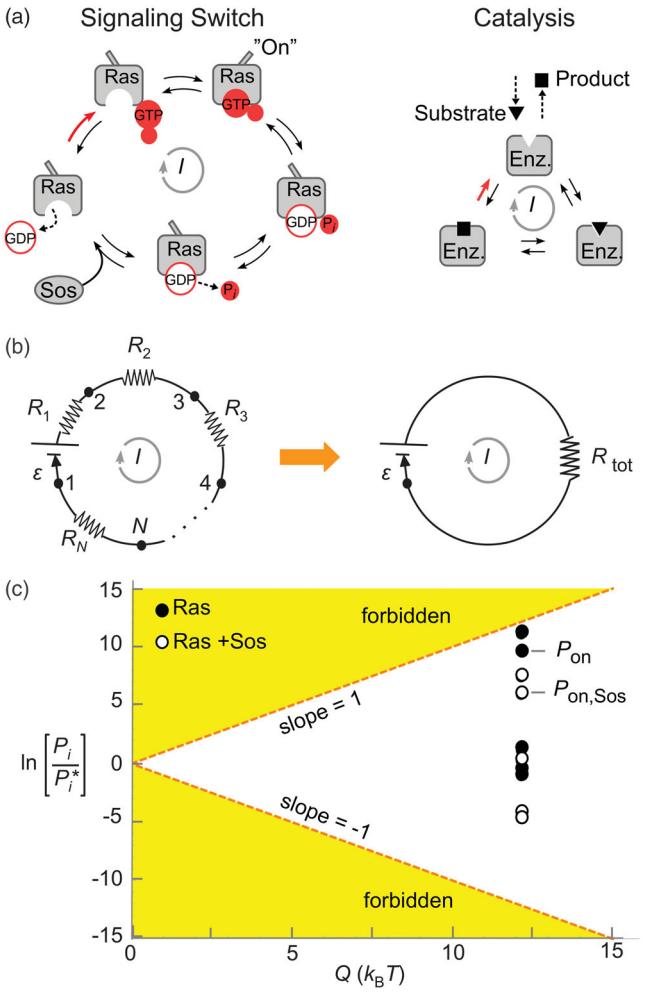

FIG. 3. Amplification limit of cyclic systems. Biomolecular systems commonly possess a cyclic state space (a), which can be mapped to circuits with resistors in series, whose total resistance is the sum of the resistors (b). The extent to which any state of such systems can be (de)amplified is bounded by the energy expenditure per cycle, as described by Eq. (8) (yellow regions are forbidden). Some states of the master signaling protein Ras approach this limit (c), including the GTP-bound ("on") state [(a), left], which is amplified orders of magnitude above equilibrium levels due to hydrolysis of GTP (parameters obtained from Refs. [28–30]). The catalyst Sos protein further tunes the on state probability, which corresponds to changing a resistor in the circuit.

cannot be obtained by energy conservation arguments because P_i could be very small despite having been amplified by many orders of magnitude. As an example, I computed the probability amplification of the master signaling G protein Ras using experimentally measured and inferred rate constants [Fig. 3(a), left] [28–30]. The states of the five-state model are shown in black or white depending on the presence of the regulatory protein Sos. Some states of this protein are close to the amplification limit, which is set by the energy released upon hydrolyzing the fuel molecule guanidine triphosphate (GTP) [Fig. 3(c)]. Note that the amplification effect of driving can be suppressed by increasing R_{12} so that $R_{\rm tot}$ dominates in Eq. (6), for example, by removing a molecule that catalyzes the reaction from state 1 to 2, and therefore $P_i \to P_i^*$. By modulating R_{12} at fixed driving, P_i can be tuned from P_i^* to the limit in Eq. (8). In contrast, changing R_{12} has no effect on the equilibrium probabilities in the undriven system. Therefore, the amplification limit also describes how the dynamic range of signaling is expanded in a driven system versus its undriven counterpart.

General reciprocal relation between response functions.—Why systems are robust to some changes and highly sensitive to others is a question of long-standing importance. I derive here a general relation between the part of a system being driven (i.e., where a battery is placed) and the sensitivity in the rest of the system (i.e., the resulting currents everywhere else). Starting with any equilibrium system, consider driving the transition from state i to j by adding α_{ij} to the equilibrium rate constant for transitioning from i to j. The driven rate constant is a monotonic function of the current that it induces, $\alpha_{ij}[I_{ij}]$. As a consequence, nonlocal currents are also induced between other states in the rest of the circuit. Denote such a nonlocal induced current, say between states m and n, as $I_{ij\to mn}$ (Fig. 4, left). In the weakly driven case, the indirectly induced currents are approximately proportional to the driving rate constant: $I_{ij\to mn} = L_{ij\to mn}\alpha_{ij}[I_{ij}]/k_{ij}$, where $L_{ij\to mn}$ is the linear response coefficient. Alternatively, if the driven transition were from m to n instead of from i to j, there would likewise be an induced current between i and j: $I_{mn\to ij} = L_{mn\to ij}\alpha_{mn}[I_{mn}]/k_{mn}$ (Fig. 4, right). Onsager famously showed that [20]

$$L_{mn\to ij} = L_{ij\to mn}. \tag{9}$$

Equation (9) is valid for observables that are linear combinations of currents. For example, in the thermoelectric effect, the electric current is induced with the same sensitivity to a temperature gradient as the heat flux is induced by an electrochemical potential [31]. However, beyond the perturbative regime, no general reciprocal relationship between cause and effect is known.

In the circuit mapping, probability fluxes obey Lorentz's reciprocity theorem [32]: the current induced between m and n due to a battery between i and j is equal to the current induced between i and j if the same battery were instead placed between m and n. This theorem is applicable because of the directional symmetry of the resistance, $R_{mn} = R_{nm}$, which holds even when the network is being driven such that the symmetry of the probability flux (i.e., detailed balance) is broken. Equation (5) and Lorentz reciprocity yields the generalized reciprocal relation that is valid arbitrarily far from equilibrium (see Supplemental Material [21]):

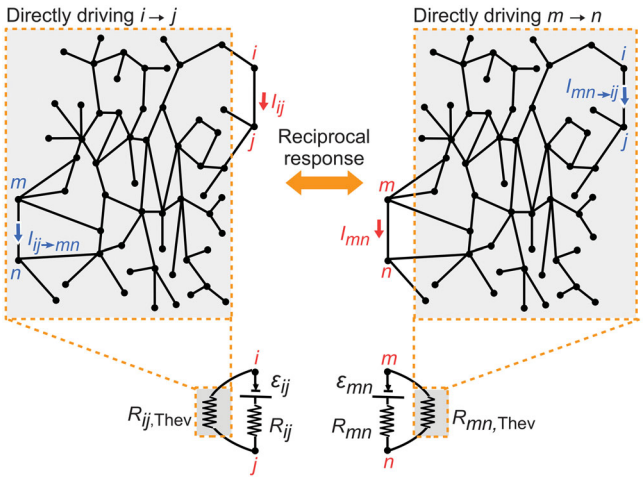

FIG. 4. Universal reciprocal relation far from equilibrium. If transition ij in the state space of system is driven (red, left) from equilibrium, there will be induced currents, for example, at mn (blue, left). If the same system were driven at mn instead (red, right), then a reciprocal current would be induced at ij (blue, right). The current response function is related to the reciprocal current response function by Eq. (10).

$$\frac{I_{ij\to mn}}{I_{ij}} = \left[\frac{R_{ij}+R_{ij,\mathrm{Thev}}}{R_{mn}+R_{mn,\mathrm{Thev}}}\right]\frac{I_{mn\to ij}}{I_{mn}}, \tag{10}$$

where the Thevenin equivalent resistance $R_{mn,\mathrm{Thev}}$ is the total resistance of the rest of the circuit as measured between states m and n (Fig. 4). Remarkably, the reciprocal current response is invariant to the degree of driving; even far from equilibrium, it is completely determined by the reference equilibrium system (in the form of Thevenin resistors) in the absence of driving. For the special case in which the system is driven close to equilibrium, $P_i/P_i^* \approx 1$, and the PFE is approximately $\alpha_{ij}[I_{ij}]/k_{ij} \approx (R_{ij}+R_{ij,\mathrm{Thev}})I_{ij}$. Substituting this and the definition of L_{ij} into Eq. (10) recovers Onsager's near-equilibrium result Eq. (9) as a special case.

It follows from this relation that, in any system, the transition ij with the maximum $R_{ij}+R_{ij,\mathrm{Thev}}$ is the one that the system is most "sensitive" to: driving this transition induces the maximum asymmetric current response with respect to every other transition of the system, regardless of the driving strength. Equation (10) can be used to tune resistances and placement of energy sources in order to optimize desired responses to driving. In light of this principle, it will be of interest to experimentally determine whether biological processes have evolved such that ATP or GTP binding occurs between states of maximal $R_{ij,\mathrm{Thev}}$.

Here, I generalize the Boltzmann distribution to a probability flow equation on a circuit whose nodes are the discrete states of any Markovian system. The circuit mapping is unique in the way in which it separates driven from undriven transitions. This allows new general conclusions to be drawn about systems far from equilibrium. Using this mapping, I show that broad classes of systems obey simple invariance relations regardless of system size and complexity. Near-equilibrium properties, such as Onsager's reciprocal relations, are revealed to be limiting cases of these results.

Probability currents are driven by differences in probability potential and external driving forces. The potential of a state is the conjugate of the probability to the exponential of the equilibrium free energy, the latter being the central concept in equilibrium thermodynamics. The currents in the circuit are conjugated to a new quantity: the resistance. This concept is not needed at equilibrium because all currents vanish in that case. However, this work demonstrates that the resistance is as important as the free energy when considering nonequilibrium systems. The resistors can be systematically combined to simplify circuits into their irreducible forms. Coarse-grained resistors in the irreducible circuit have two useful properties. First, being a function of the equilibrium parameters, they remain constant regardless of the extent of driving, and so can give insight into the invariant behavior of the system regardless of its numerical value. Second, they can be obtained without knowledge of their constituent microscopic processes by measuring the net current through the coarse-grained resistor. This approach to simplification [Figs. 2(c) and 2(d)], commonly applied to electronic circuits [24], is especially useful for molecular biology, for which a sparse subset of transitions are directly coupled to an external energy supply, consequently driving the remainder of the transitions away from equilibrium.

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