Steady-state balance conditions for molecular motor cycles and stochastic nonequilibrium processes

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Abstract – Molecular motors and nanomachines are considered that are coupled to exergonic processes which provide energy input to these motors and allow them to perform work. The motor dynamics is described by continuous-time Markov processes on a discrete state space, which can contain an arbitrary number of cycles consisting of two dicycles with opposite orientation. For the steady state of such a motor, the statistical entropy produced during the completion of each dicycle is expressed in terms of its transition rates. Identifying this statistical entropy with the heat released by the motor and using the first law of thermodynamics, we derive steady-state balance conditions that generalize the well-known detailed balance conditions in equilibrium. Our derivation is rather general and applies to any nonequilibrium system described as a Markov process. For molecular motors, these balance conditions depend on the external load force and can be decomposed into a zero-force and a force-dependent part.

Introduction. – Living cells contain a large number of molecular motors: membrane pumps, cytoskeletal motors, growing filaments, and assemblers such as polymerases and ribosomes [1]. In many cases, these nanomachines are driven by the energy released from fuel molecules such as ATP. The corresponding catalytic reactions have to be exergonic and to occur primarily in the forward direction in order to break detailed balance and time-reversal symmetry. The coupling of the motor to these nonequilibrium reactions provides energy which is converted into conformational transformations of the motor and enables it to perform work. This chemomechanical coupling involves three aspects of randomness [2]: i) each chemical reaction represents a stochastic process since the fuel molecules are delivered by diffusion and the reshuffling of the chemical bonds has an intrinsically stochastic character; ii) these machines may also exhibit several chemical pathways or motor cycles as recently proposed for the cytoskeletal motor kinesin [3]; and iii) because of their small size, the molecular conformations of these machines exhibit strong thermal fluctuations.

In order to obtain a useful description of such a motor, we will focus on the different chemical states, denoted by $\lfloor i \rfloor$ with $i = 1, 2., \ldots N_s$, which are involved in the catalytic reaction that drives the motor. As a concrete example, consider a motor protein that consumes ATP. Each protein domain that is able to catalyze ATP hydrolysis can then be in three different states corresponding to bound ATP, bound ADP, and no bound ATP or ADP[1]. Thus, if the molecular motor has k catalytic domains, it can attain $N_s = 3^k$ different chemical states and undergo transitions between these states.

It is useful to visualize the motor's state space as a network graph for which the vertices represent the N_s states of the motor; an example is shown in fig. 1. Every pair $\lfloor i \rfloor$ and $\lfloor j \rfloor$ of states is connected by two directed edges or di-edges corresponding to the forward transition $|ij\rangle$ from $\lfloor i \rfloor$ to $\lfloor j \rfloor$ and the backward transition $|ji\rangle$ from $\lfloor j \rfloor$ to $\lfloor i \rfloor$. In fig. 1, these two di-edges are combined into the undirected edge $\langle ij \rangle$. In general, the motor may undergo a chemical transition in which one of the catalytic motor domains changes its chemical composition or a mechanical transition corresponding to a mechanical step (or substep). In fig. 1, chemical and mechanical transitions are indicated by solid and broken lines, respectively.

Nonequilibrium steady states are intimately related to *cycles* in state space and nonzero fluxes along these

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[1]The hydrolysis of ATP leads to the reaction products ADP and inorganic P. An extended description includes bound ADP-P as a fourth state which implies $N_s = 4^k$.
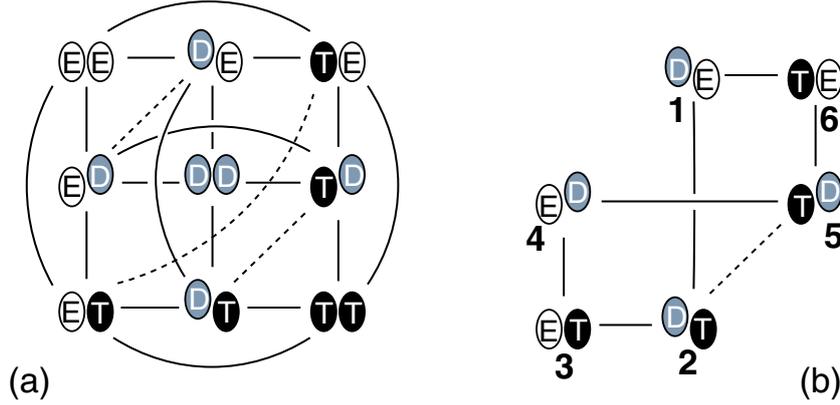
Fig. 1: (a) Network graph with 9 states for a molecular motor with two catalytic domains, each of which can be empty (E), or bind an ATP (T) or ADP (D) molecule. This network contains 21 edges corresponding to 18 chemical forward and backward transitions (solid lines) as well as 3 mechanical forward and backward steps (broken lines); and (b) reduced state space with 6 states $\lfloor i \rfloor$ with $i = 1, 2, \ldots, 6$ obtained from the 9-state network in (a) by omitting the three states E-E, T-T, and D-D. This network contains 7 edges $\langle ij \rangle$ corresponding to 6 chemical transitions (full lines) plus 1 mechanical transition (broken line).

cycles [4–6]. In order to be precise, we will distinguish the undirected cycle $\mathcal{C}_\nu = \langle i_1, i_2, \ldots, i_n, i_1 \rangle$, which consists of the edges $\langle i_1 i_2 \rangle$, $\langle i_2 i_3 \rangle$, ..., and $\langle i_n i_1 \rangle$, from the directed cycles or *dicycles* $\mathcal{C}_\nu^+ = \lfloor i_1, i_2, \ldots, i_n, i_1 \rangle$ and $\mathcal{C}_\nu^- = \lfloor i_1, i_n, \ldots, i_2, i_1 \rangle$. The network graph in fig. 1(a) contains a large number of different cycles whereas the one in fig. 1(b) has only three cycles, namely $\langle 2, 5, 6, 1, 2 \rangle$, $\langle 5, 2, 3, 4, 5 \rangle$, and $\langle 1, 2, 3, 4, 5, 6, 1 \rangle$.

Main conclusions. – Since our discussion is necessarily somewhat formal, we first summarize our main conclusions. The dynamics of the motor is described by a continuous-time Markov process [7,8] with transition rates ω_{ij} from state $\lfloor i \rfloor$ to state $\lfloor j \rfloor$. We consider the statistical entropies $\Delta S(\mathcal{C}_\nu^+)$ and $\Delta S(\mathcal{C}_\nu^-)$, which are produced, in the steady state, during the completion of dicycle $\mathcal{C}_\nu^+$ and $\mathcal{C}_\nu^-$, respectivly, and show that these dicycle entropies satisfy the simple relation

$$\Delta S(\mathcal{C}_\nu^+) = k_B \sum_{\lfloor ij \rangle}^{\nu, +} \ln(\omega_{ij}/\omega_{ji}) = -\Delta S(\mathcal{C}_\nu^-), \quad (1)$$

where the superscipt $\nu, +$ at the summation sign indicates a summation over all di-edges $\lfloor ij \rangle$ of dicycle $\mathcal{C}_\nu^+$.

Each state $\lfloor i \rfloor$ of the motor represents an ensemble of molecular conformations that differ in thermally excited vibrational modes. The corresponding internal energy will be denoted by U_i. During the transition $\lfloor ij \rangle$, the internal energy can change because of i) energy input $E_{\text{ch},ij}$ arising from the coupling to the exergonic chemical reaction, ii) mechanical work $W_{\text{me},ij}$, which the motor performs against an external force, and iii) heat Q_{ij}, which the motor releases into the surrounding medium. Conservation of energy implies $\Delta U_{ij} \equiv U_j - U_i = E_{\text{ch},ij} - W_{\text{me},ij} - Q_{ij}$. The special case $\Delta U_{ij} = 0$ has been considered in ref. [9] for simple motor models with a single cycle. In general, the energy input $E_{\text{ch},ij}$ may be partially *stored* in the motor molecule after the transition $\lfloor ij \rangle$, which implies

$\Delta U_{ij} > 0$, and this stored energy may be transformed into work and/or heat during a later transition $\lfloor i'j' \rangle$, which implies $\Delta U_{i'j'} < 0$. However, because the internal energy is a state property, its change, $\Delta U(\mathcal{C}_\nu^+)$, along any dicycle $\mathcal{C}_\nu^+$ must satisfy

$$\Delta U(\mathcal{C}_\nu^+) = E_{\text{ch}}(\mathcal{C}_\nu^+) - W_{\text{me}}(\mathcal{C}_\nu^+) - Q(\mathcal{C}_\nu^+) = 0, \quad (2)$$

where the three terms $E_{\text{ch}}(\mathcal{C}_\nu^+)$, $W_{\text{me}}(\mathcal{C}_\nu^+)$, and $Q(\mathcal{C}_\nu^+)$ represent the energy input, work performed, and heat released during the completion of $\mathcal{C}_\nu^+$, respectively. We now identify the heat released by the motor with the statistical entropy produced by it. A combination of (2) and (1) then leads to the steady-state balance conditions

$$\sum_{\lfloor ij \rangle}^{\nu, +} \ln \left(\frac{\omega_{ij}}{\omega_{ji}} \right) = [E_{\text{ch}}(\mathcal{C}_\nu^+) - W_{\text{me}}(\mathcal{C}_\nu^+)]/k_B T, \quad (3)$$

which provide relations between the transition rates ω_{ij}, the chemical energy input E_{ch}, and the mechanical work W_{me} for any dicycle of the network. In equilibrium, all terms on the right-hand side of this equation vanish, and we recover the well-known conditions of detailed balance, which are called Wegscheider conditions [10] in the context of chemical kinetics.

The mechanical work is determined by external load forces experienced by the motor and vanishes in the absence of such forces. This implies that one can decompose the steady-state balance conditions (3) into a zero-force and a force-dependent part as we will show explicitly for the case of cytoskeletal motors. At the end of this article, we will also discuss the number of independent balance conditions and various extensions to other nonequilibrium processes.

Dynamics in state space. – Next, we give a precise definition of our motor models. When the motor arrives at a certain state $\lfloor i \rfloor$, it occupies this state for a certain

sojourn (or holding) time τ_i, which is a random variable that is governed by the probability distribution $\mathcal{P}(\tau_i) = (1/\langle\tau_i\rangle)\exp(-\tau_i/\langle\tau_i\rangle)$, where $\langle\tau_i\rangle$ denotes the average sojourn time [8]. When the motor leaves the state $\lfloor i\rfloor$, it jumps to state $\lfloor j\rfloor$ with probability π_{ij}. The probability $P_i(t)$ to find the motor in state $\lfloor i\rfloor$ at time t is then governed by the Master equation

$$\frac{\mathrm{d}}{\mathrm{d}t}P_i = -\sum_j \Delta J_{ij},$$

$$\text{with} \quad \Delta J_{ij} \equiv P_i\omega_{ij} - P_j\omega_{ji} = -\Delta J_{ji}$$

$$\text{and} \quad \omega_{ij} = \pi_{ij}/\langle\tau_i\rangle. \tag{4}$$

The *steady state* is characterized by probabilities P_i^{st} with $\mathrm{d}P_i^{\mathrm{st}}/\mathrm{d}t = 0$ which implies

$$\sum_j \Delta J_{ij}^{\mathrm{st}} = \sum_j \left(P_i^{\mathrm{st}}\omega_{ij} - P_j^{\mathrm{st}}\omega_{ji}\right) = 0. \tag{5}$$

This relation provides N_{s} linear equations for the probabilities P_i^{st} which can be solved by linear algebra, see, *e.g.*, [11,12] or, more conveniently, by a graph-theoretic method [2,13–15].

In order to calculate the frequencies of dicycle completions in the steady state, we start from the action functional A as defined by Lebowitz and Spohn [16]. Thus, consider a directed walk or trajectory $\mathcal{T}^+ \equiv |i_1, i_2\ldots, i_m\rangle$ on the network graph together with the time-reversed walk $\mathcal{T}^- \equiv |i_m, i_{m-1}\ldots, i_1\rangle$. Each walk consists of a connected sequence of di-edges $|ij\rangle$. The action functional A is then defined by

$$\exp[A(\mathcal{T}^+)] \equiv \prod_{|ij\rangle\in\mathcal{T}^+} \omega_{ij} \Big/ \prod_{|ij\rangle\in\mathcal{T}^-} \omega_{ij} = \exp[-A(\mathcal{T}^-)], \tag{6}$$

where the product in the numerator and denominator runs over all di-edges of the walk $\mathcal{T}^+$ and $\mathcal{T}^-$, respectively. The probabilities $\Omega(\mathcal{T}^+)$ and $\Omega(\mathcal{T}^-)$ for the two walks $\mathcal{T}^+$ and $\mathcal{T}^-$ are then related to the action functional A via $\Omega(\mathcal{T}^+)/\Omega(\mathcal{T}^-) = (P_1^{\mathrm{st}}/P_m^{\mathrm{st}})\exp[A(\mathcal{T}^+)]$ [16]. This relation simplifies for closed walks $\mathcal{T}_c^+$ which are characterized by $i_m \equiv i_1$ and, thus, by $P_1^{\mathrm{st}} = P_m^{\mathrm{st}}$. Indeed, for any closed trajectory $\mathcal{T}_c^+$ that goes through the dicycle $\mathcal{C}_\nu^+$ only once and does not go through any other dicycle, one obtains the probability ratio

$$\frac{\Omega(\mathcal{T}_c^+)}{\Omega(\mathcal{T}_c^-)} = \frac{\Omega(\mathcal{C}_\nu^+)}{\Omega(\mathcal{C}_\nu^-)} = \exp[A(\mathcal{C}_\nu^+)] = \prod_{|ij\rangle}^{\nu,+}(\omega_{ij}/\omega_{ji}), \tag{7}$$

where the superscript $\nu, +$ at the product sign indicates a product over all di-edges $|ij\rangle$ contained in the dicycle $\mathcal{C}_\nu^+$. In general, such a closed trajectory $\mathcal{T}_c^+$ will consist of the dicycle $\mathcal{C}_\nu^+$ together with various tree-like excursions away from it as well as multiple walks along partial segments of $\mathcal{C}_\nu^+$. However, all transition rates apart from those

corresponding to one completion of $\mathcal{C}_\nu^+$ and $\mathcal{C}_\nu^-$ cancel in the probability ratio (7).

Cycle decomposition of fluxes. – The relation for the probability ratio $\Omega(\mathcal{C}_\nu^+)/\Omega(\mathcal{C}_\nu^-)$ contained in (7) can also be derived from the explicit solution of (5) [17,18]. This latter derivation is based on the cycle fluxes as given by [2,14,17]

$$J^{\mathrm{st}}(\mathcal{C}_\nu) = J^{\mathrm{st}}(\mathcal{C}_\nu^+) - J^{\mathrm{st}}(\mathcal{C}_\nu^-)$$

$$\text{with} \quad J^{\mathrm{st}}(\mathcal{C}_\nu^d) = \left(\prod_{|ij\rangle}^{\nu,d} \omega_{ij}\right) \Upsilon(\mathcal{C}_\nu)/\Omega \quad \text{and} \quad d \equiv \pm. \tag{8}$$

Both $\Upsilon(\mathcal{C}_\nu)$ and Ω are multilinear polynomials of the transition rates ω_{ij}; the polynomial $\Upsilon(\mathcal{C}_\nu)$ is identical for the two dicycles $\mathcal{C}_\nu^+$ and $\mathcal{C}_\nu^-$; the polynomial Ω is a dicycle-independent normalization factor. The excess fluxes $\Delta J_{ij}^{\mathrm{st}}$ can now be expressed as

$$\Delta J_{ij}^{\mathrm{st}} = \sum_\nu \epsilon_{ij,\nu} J^{\mathrm{st}}(\mathcal{C}_\nu) = \sum_\nu \epsilon_{ij,\nu} \left(J^{\mathrm{st}}(\mathcal{C}_\nu^+) - J^{\mathrm{st}}(\mathcal{C}_\nu^-)\right), \tag{9}$$

where the antisymmetric symbol $\epsilon_{ij,\nu} = -\epsilon_{ji,\nu}$ is equal to $+1$ and -1 for $|ij\rangle \in \mathcal{C}_\nu^+$ and $|ij\rangle \in \mathcal{C}_\nu^-$, respectively, and $\epsilon_{ij,\nu} = 0$, otherwise.

The dicycle fluxes $J^{\mathrm{st}}(\mathcal{C}_\nu^d)$ determine the average times for dicycle completion. Thus, let us follow the motor's walk for a long time period Δt. The motor will then pass successively through many dicycles and we can count the number of times, $N_{\Delta t}(\mathcal{C}_\nu^d)$, that it passed through the dicycle $\mathcal{C}_\nu^d$. Thus, $N_{\Delta t}(\mathcal{C}_\nu^d)$ represents the absolute frequency of completed dicycles $\mathcal{C}_\nu^d$ within the time period Δt. These frequencies are related to the dicycle fluxes via $N_{\Delta t}(\mathcal{C}_\nu^d)/\Delta t \approx J^{\mathrm{st}}(\mathcal{C}_\nu^d)$ for large Δt which implies the average time $\tau(\mathcal{C}_\nu^d) = 1/J^{\mathrm{st}}(\mathcal{C}_\nu^d)$ for the completion of the dicycle $\mathcal{C}_\nu^d$ [17,18].

Statistical entropy and entropy production. – The statistical entropy $S\{P_i\}$ of the motor is defined by $S\{P_i\} \equiv -k_B \sum_i P_i \ln(P_i)$, and its time derivative can be written in the form $\frac{\mathrm{d}}{\mathrm{d}t}S\{P_i\} = \sigma_{\mathrm{pr}} + \sigma_{\mathrm{fl}}$ with the entropy production rate σ_{pr} and the entropy flux term σ_{fl}, which represents the heat flux from the surrounding medium, as given by [15,16,19,20]

$$\sigma_{\mathrm{pr}} \equiv \tfrac{1}{2}k_B \sum_{ij} \Delta J_{ij} \ln\left(\frac{P_i\omega_{ij}}{P_j\omega_{ji}}\right)$$

$$\text{and} \quad \sigma_{\mathrm{fl}} \equiv -\tfrac{1}{2}k_B \sum_{ij} \Delta J_{ij} \ln\left(\frac{\omega_{ij}}{\omega_{ji}}\right). \tag{10}$$

In the steady state with $\frac{\mathrm{d}}{\mathrm{d}t}S = 0$, one then obtains the entropy production rate $\sigma_{\mathrm{pr}}^{\mathrm{st}} = -\sigma_{\mathrm{fl}}^{\mathrm{st}} = k_B \sum \Delta J_{ij}^{\mathrm{st}} \times \ln(\omega_{ij}/\omega_{ji})$ where the sum runs over all edges $\langle ij\rangle$ of the network graph. We now insert the cycle decomposition

for ΔJ_{ij} as given by (9) into the expression for $\sigma_{\mathrm{pr}}^{\mathrm{st}}$ which leads to

$$\sigma_{\mathrm{pr}}^{\mathrm{st}} = k_B \sum_{\nu} J^{\mathrm{st}}(\mathcal{C}_{\nu}) \sum_{\langle ij \rangle} \epsilon_{ij,\nu} \ln(\omega_{ij}/\omega_{ji})$$

$$= k_B \sum_{\nu} J^{\mathrm{st}}(\mathcal{C}_{\nu}) A(\mathcal{C}_{\nu}^+). \qquad (11)$$

with the dicycle action $A(\mathcal{C}_{\nu}^+)$ as in (7). Combining (11) with $J^{\mathrm{st}}(\mathcal{C}_{\nu}) = J^{\mathrm{st}}(\mathcal{C}_{\nu}^+) - J^{\mathrm{st}}(\mathcal{C}_{\nu}^-)$, we obtain

$$\sigma_{\mathrm{pr}}^{\mathrm{st}} = \sum_{\nu} \left(\sigma^{\mathrm{st}}(\mathcal{C}_{\nu}^+) - \sigma^{\mathrm{st}}(\mathcal{C}_{\nu}^-) \right)$$

$$\text{with} \quad \sigma^{\mathrm{st}}(\mathcal{C}_{\nu}^d) \equiv J^{\mathrm{st}}(\mathcal{C}_{\nu}^d) \, k_B \sum_{|ij\rangle}^{\nu,d} \ln(\omega_{ij}/\omega_{ji}). \qquad (12)$$

Using the explicit solution of the steady-state equations (5), Hill and Simmons [4,5] have previously shown that the expression (11) applies to several specific models of biochemical kinetics. In these latter studies, the dicycle actions $A(\mathcal{C}_{\nu}^+)$ were interpreted as "thermodynamic forces" $X_{\nu}^+ \equiv k_B T A(\mathcal{C}_{\nu}^+)$. In addition, Qian [6] has obtained a relation that is equivalent to (12) and applied it to a 3-state Markov process with a single cycle.

We now integrate the entropy production rate $\sigma^{\mathrm{st}}(\mathcal{C}_{\nu}^d)$ for dicycle $\mathcal{C}_{\nu}^d$ as given by (12) over the average time $\tau(\mathcal{C}_{\nu}^d) = 1/J(\mathcal{C}_{\nu}^d)$ for completing this dicycle, which cancels the factor $J(\mathcal{C}_{\nu}^d)$ on the right-hand side of (12). In this way, we find that the entropies produced by the completion of the dicycles $\mathcal{C}_{\nu}^+$ and $\mathcal{C}_{\nu}^-$ satisfy the simple relations (1) which imply that these entropies are odd under time reversal. Thus, our derivation reveals that the thermodynamic force X_{ν}^+ considered in refs. [4,5] is, in fact, T times the statistical entropy produced per completed dicycle.

Seifert [21,22] has recently proposed an evolution equation for the entropy production that is defined for single walks (or trajectories). If the walk jumps at the discrete times $t = t_m$ from state i_m to state j_m, this evolution equation can be written in the form $\frac{\mathrm{d}}{\mathrm{d}t} S_1 = \sum_m \delta(t - t_m) S_{i_m j_m}$ with $S_{ij} \equiv k_B \ln(\omega_{ij}/\omega_{ji})$. If one integrates the evolution equation in time along any closed walk that goes through the dicycle $\mathcal{C}_{\nu}^d$ only once and does not go through any other dicycle, one recovers relation (1). Thus, the evolution equation as proposed in [21,22] is consistent with the dicycle entropies as derived here using *only* steady-state properties. One should note, however, that the single edge term $k_B \ln(\omega_{ij}/\omega_{ji})$, which is identified with the entropy change S_{ij} during the transition $|ij\rangle$ in [21,22], is interpreted in terms of different thermodynamic potentials in [4,5,23].

Example: Cytoskeletal motors. – As an example, we now consider cytoskeletal motors such as kinesin or dynein which catalyze ATP hydrolysis and perform discrete steps along cytoskeletal filaments, compare fig. 1. Each dicycle then contains $n_{\mathrm{h}}(\mathcal{C}_{\nu}^d) \geqslant 0$ transitions that involve ATP hydrolysis as well as $n_{\mathrm{s}}(\mathcal{C}_{\nu}^d) \geqslant 0$ transitions

that correspond to ATP synthesis. The chemical energy input per completed dicycle now depends on the molar concentrations [ATP], [ADP], and [P] and has the explicit form

$$E_{\mathrm{ch}}(\mathcal{C}_{\nu}^d) = [n_{\mathrm{h}}(\mathcal{C}_{\nu}^d) - n_{\mathrm{s}}(\mathcal{C}_{\nu}^d)] \Delta\mu$$

$$\text{with} \quad \Delta\mu \equiv k_B T \ln(K_{eq}[ATP]/[ADP][P]), \qquad (13)$$

where $\Delta\mu$ represents the energy change per hydrolyzed ATP molecule and K_{eq} is the corresponding equilibrium constant.

In addition, each dicycle leads to $m_{\mathrm{f}}(\mathcal{C}_{\nu}^d) \geqslant 0$ forward mechanical steps and to $m_{\mathrm{b}}(\mathcal{C}_{\nu}^d) \geqslant 0$ backward mechanical steps. For simplicity, let us focus on motors such as kinesin that have a fixed step size ℓ. In the presence of an external load force, F, the mechanical work performed by the motor during one completed dicycle is then given by

$$W_{\mathrm{me}}(\mathcal{C}_{\nu}^d) = [m_{\mathrm{f}}(\mathcal{C}_{\nu}^d) - m_{\mathrm{b}}(\mathcal{C}_{\nu}^d)] \, \ell \, F. \qquad (14)$$

It is now convenient to parametrize the motor's transition rates ω_{ij} according to

$$\omega_{ij} = \omega_{ij}(F) \equiv \omega_{ij,0} \, \Phi_{ij}(F) \quad \text{with} \quad \Phi_{ij}(0) \equiv 1. \qquad (15)$$

For $F = 0$, the mechanical work vanishes, and the condition (3) becomes

$$\sum_{|ij\rangle}^{\nu,+} \ln \left(\frac{\omega_{ij,0}}{\omega_{ji,0}} \right) = \left(n_{\mathrm{h}}(\mathcal{C}_{\nu}^+) - n_{\mathrm{s}}(\mathcal{C}_{\nu}^+) \right) \frac{\Delta\mu}{k_B T}, \qquad (16)$$

which relates the zero-force transition rates $\omega_{ij,0}$ to the free energy change $\Delta\mu$ per hydrolyzed ATP molecule. The models of biochemical kinetics considered in refs. [4,5] provide examples for relation (16). Substracting condition (16) from condition (3), we also obtain

$$\sum_{|ij\rangle}^{\nu,+} \ln \left(\frac{\Phi_{ij}(F)}{\Phi_{ji}(F)} \right) = - [m_{\mathrm{f}}(\mathcal{C}_{\nu}^+) - m_{\mathrm{b}}(\mathcal{C}_{\nu}^+)] \, \ell \, F / k_B T, \qquad (17)$$

which relates the transition rate factors $\Phi_{ij}(F)$ to the step size ℓ and the external force F.

In this way, we have decomposed the steady-steady balance condition (3) into two independent parts. The first part (16) imposes one condition per cycle on the zero-force transition rates $\omega_{ij,0}$. The second part (17) imposes one condition per cycle on the F-dependent transition rate factors $\Phi_{ij}(F)$. Both for $F = 0$ and $F \neq 0$, the number of linearly independent conditions is equal to the number N_{fc} of so-called fundamental cycles of the network, a property that has been proven in [24] for detailed balance. For a network graph with N_{s} states and N_{e} edges, the number of fundamental cycles is equal to $N_{\mathrm{fc}} = N_{\mathrm{e}} - N_{\mathrm{s}} + 1$. Thus, the $2N_{\mathrm{e}}$ transition rates ω_{ij} have to satisfy N_{fc} balance conditions. For networks with $N_{\mathrm{e}} \gg N_{\mathrm{s}}$ only about half of the transition rates can be varied independently from each other.

Summary and outlook. – In summary, we have derived steady state balance conditions as given by (3), (16), and (17) for molecular motors and biomimetic nanomachines that relate the transition rates ω_{ij} between different motor states to the input of chemical energy and to the mechanical work per completed dicycle. Our derivation was based on i) the identification of the statistical dicycle entropies as given by (1) with the heat released by the motor during the completion of the corresponding dicycles and ii) the 1st law of thermodynamics when applied to these dicycles. In principle, both the transition rates ω_{ij} and the energetic terms on the right hand side of (3), (16), and (17) can be measured. If such a complete set of experiments were available for a certain motor, one could use the balance conditions to estimate the experimental accuracy. In practise, some of the transition rates will be difficult to measure, and the balance conditions can then be used to estimate the values of the unknown rates.

We have recently applied this latter strategy to the cytoskeletal motor kinesin [25]. One important consequence of our analysis is that the stall force of the motor is determined by the flux balance of two different cycles that govern the forward and backward mechanical step and both involve the hydrolysis of one ATP molecule as proposed in ref. [3]. This differs from previous unicycle models in which the stall force was determined by the flux balance between the two dicycles of the same cycle. The latter flux balance is, however, not possible for small ADP concentrations as typically considered in motility assays.

It is straightforward to include other energetic processes into the steady state balance conditions. Two examples are i) energy input E_{em} arising from electromagnetic fields, *i.e.*, from the adsorption of photons and ii) work W_{ec} against an electrochemical potential. If the motor is also coupled to these two processes, one obtains the generalized balance conditions

$$\sum_{|ij\rangle}^{\nu,d} \ln\left(\frac{\omega_{ij}}{\omega_{ji}}\right) =$$

$$[E_{\mathrm{ch}}(\mathcal{C}_\nu^d) + E_{\mathrm{em}}(\mathcal{C}_\nu^d) - W_{\mathrm{me}}(\mathcal{C}_\nu^d) - W_{\mathrm{ec}}(\mathcal{C}_\nu^d)]/k_B T. \quad (18)$$

One interesting example is provided by the molecular motor F_0F_1 ATP synthase which uses an ion gradient to synthesize ATP. Finally, our derivation of the steady-state balance conditions is rather general and can be applied to any nonequilibrium system that is described by a continuous-time Markov process.

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