Generalized Einstein or Green-Kubo Relations for Active Biomolecular Transport

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For driven Markovian dynamics on a network of (biomolecular) states, the generalized mobilities, i.e., the response of any current to changes in an external parameter, are expressed by an integral over an appropriate current-current correlation function and thus related to the generalized diffusion constants. As only input, a local detailed balance condition is required which is typically even valid for biomolecular systems operating deep in the nonequilibrium regime.

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Introduction.—Close to equilibrium, transport coefficients like the mobility, conductivity or viscosity, quantifying the response of a system to an external field or perturbation, can be expressed by equilibrium correlation functions. The Stokes-Einstein relation between the mobility and the diffusion constant of a spherical particle is arguably the oldest and best known example of such a Green-Kubo relation [1]. Both mobility and diffusion constant are still well-defined even for a nonequilibrium steady state (NESS) of an open or driven system in which stationary currents lead to permanent dissipation. In such a state, the Stokes-Einstein relation no longer holds true. The difference between diffusion constant and mobility, however, can be expressed by an integral over an experimentally measurable correlation function [2].

In the present Letter, we investigate the relation between a mobility or transport coefficient and the corresponding dispersion or fluctuations for any current in an arbitrary driven system with special focus on biomolecular transport like the one mediated by molecular motors or ion pumps. The essential characteristics of such transport is that even though the system is driven, typically by nonbalanced chemical reaction involving nucleotides like ATP or ADP, it takes place in a well-defined thermal environment. This fact imposes a constraint on the ratio between forward and backward rates for any mesoscopic transition that will allow us to express the difference between mobility and dispersion in a physically transparent way. On the technical level, we build on the recent derivation of a general fluctuation-dissipation theorem for NESSs [3–6]. By directly working in the NESS, our approach is complementary to work that invokes the fluctuation theorem for deriving nonlinear response coefficients in higher order expansions around equilibrium [7,8]. Moreover, it goes beyond similar relations obtained for genuine diffusive spatial transport [9,10] since we require no Euclidean metric and hence the notion of a locally comoving frame is not available. Our results will therefore be applicable not only to any discrete model for a molecular motor or ion pump (see, e.g., [11–14] and references therein) but also to driven (bio)chemical reaction networks and their response to changing chemical conditions [15,16]. As a simple illustration will show, a misguided rewriting of our additive relationship between mobility and dispersion in terms of a multiplicative "effective temperature" could easily lead even to negative values for the latter as found for various active biomolecular systems, see, e.g., [17,18].

System.—We describe the system by a set of discrete states $\{n\}$. At time t, the system is in a state $n(t)$ jumping at discrete times t_j from state n_j^- to state n_j^+. A transition between state m and state n occurs with a rate w_{mn}. With each transition $m \to n$, we associate transport of a quantity $d^\alpha_{mn} = -d^\alpha_{nm}$ leading to a microscopic current

$$j_\alpha(t) \equiv \sum_j \delta(t - t_j) d^\alpha_{n_j^- n_j^+}. \tag{1}$$

The transition rates between the states depend on a set of external parameters $\{h_\beta\}$. We make no particular assumptions on the parameter dependence of the individual transition rates but only require that the ratio between forward and backward rates obeys the typical "local detailed balance" (LDB) condition

$$\frac{w_{mn}(\{h_\beta\})}{w_{nm}(\{h_\beta\})} = \frac{w_{mn}(\{0\})}{w_{nm}(\{0\})} \exp\left[\sum_\beta h_\beta d^\beta_{mn}/T\right], \tag{2}$$

which implies for the logarithmic derivatives, or "sensitivities," $r^\beta_{mn} \equiv T\partial_{h_\beta} \ln w_{mn}$, the crucial relation

$$r^\beta_{mn} - r^\beta_{nm} = d^\beta_{mn}. \tag{3}$$

Here, and throughout the Letter, we set Boltzmann's constant $k_B \equiv 1$. Examples for pairs of an external parameter h_α and a conjugate distance d^α are (i) force f and spatial distance d, (ii) chemical potential μ_α and number d^α of consumed (or, if negative, produced) molecules of type α (like ATP and ADP) and (iii) potential difference $\Delta\phi$ and transported electrical charge q. These choices are relevant to molecular motors (i–ii) and ion pumps (ii–iii), respectively. In all these cases, the LDB condition is usually assumed not only for small deviations from equilibrium but also for finite values of the fields $\{h_\beta\}$.

For constant external parameters $\{h_\beta\}$, the system reaches a stationary state in which $p_m \equiv \langle \delta_{n(t)m} \rangle$ denotes the probability to find it in the particular state m. Throughout the Letter, the angular brackets $\langle \cdots \rangle$ denote averages in this stationary state. If the system operates in a genuine NESS at least one pair of directed probability currents

$$K_{mn} \equiv p_m w_{mn} - p_n w_{nm} = -K_{nm} \tag{4}$$

is nonzero. Consequently, some of the currents have a nonzero mean

$$j_\alpha \equiv \langle j_\alpha(t) \rangle = \sum_{mn} p_m w_{mn} d^\alpha_{mn} = \sum_{mn} K_{mn} d^\alpha_{mn}/2. \tag{5}$$

We will need a second type of current derived from a local variable

$$\nu_\alpha(t) = \sum_m \delta_{n(t)m} \nu^\alpha_m \quad \text{with} \quad \nu^\alpha_m \equiv \sum_k K_{mk} r^\alpha_{mk}/p_m \tag{6}$$

which could be called a "sensitivity-weighted" current. It generalizes the mean local velocity found in this context for Langevin systems [9] to arbitrary networks. Positive contributions to $\nu_\alpha(t)$ arise from links for which the directed probability current and the sensitivity have the same sign. The dimension of $\nu_\alpha(t)$ justifies calling it a current. Moreover, its mean is equal to the ordinary current since $\langle \nu_\alpha(t) \rangle = \sum_{mn} K_{mn} r^\alpha_{mn} = j_\alpha$ where we use (3) from above.

Generalized Green-Kubo relations.—The aim of generalizing the Einstein or Green-Kubo relations to nonequilibrium processes requires that we express both the generalized diffusion constants, or dispersions, and the generalized mobilities by correlation functions involving currents. The dispersions given by

$$D_{\alpha\beta} \equiv \lim_{t\to\infty} \frac{1}{2t} \int_0^t dt' \int_0^t dt'' \langle [j_\alpha(t') - j_\alpha][j_\beta(t'') - j_\beta] \rangle \tag{7}$$

characterize the integrated fluctuations around the mean currents. By isolating the diagonal in this double integral and exploiting stationarity, we can rewrite the dispersions as

$$D_{\alpha\beta} = \int_{0^+}^\infty dt \langle [j_\alpha(t) - j_\alpha][j_\beta(0) - j_\beta] \rangle + D^{\text{loc}}_{\alpha\beta}. \tag{8}$$

The lower boundary 0^+ at the integral indicates that no deltalike contributions at $t = 0$ should be picked up since those are captured by the time-local contribution

$$D^{\text{loc}}_{\alpha\beta} \equiv \lim_{\epsilon\to 0} (1/2\epsilon) \int_{-\epsilon/2}^{\epsilon/2} dt \langle j_\alpha(t) j_\beta(0) \rangle \tag{9}$$

$$= (1/2) \sum_{mn} p_m w_{mn} d^\alpha_{mn} d^\beta_{mn}. \tag{10}$$

The generalized mobilities $\kappa_{\alpha\beta} \equiv \partial_{h_\beta} j_\alpha$ quantify the dependence of the mean current on an external parameter. As our main result, we will prove below that they can also be expressed by an integral involving a correlation function of the currents just introduced and a local term in the form

$$\kappa_{\alpha\beta} = \int_{0^+}^\infty dt \langle j_\alpha(t)[j_\beta(0) - \nu_\beta(0)] \rangle / T + \kappa^{\text{loc}}_{\alpha\beta} \tag{11}$$

where

$$\kappa^{\text{loc}}_{\alpha\beta} \equiv \sum_{mn} d^\alpha_{mn} p_m w_{mn} r^\beta_{mn}/T. \tag{12}$$

Hence, the difference between the dispersion and mobility tensors can be expressed as

$$I_{\alpha\beta} = D_{\alpha\beta} - T\kappa_{\alpha\beta} = \int_0^\infty dt \langle j_\alpha(t)(\nu_\beta(0) - j_\beta) \rangle + I^{\text{loc}}_{\alpha\beta} \tag{13}$$

with the local contribution

$$I^{\text{loc}}_{\alpha\beta} = D^{\text{loc}}_{\alpha\beta} - T\kappa^{\text{loc}}_{\alpha\beta} = -\sum_{m<n} d^\alpha_{mn} K_{mn} (r^\beta_{mn} + r^\beta_{nm})/2, \tag{14}$$

where the notation $\sum_{m<n}$ indicates that each link is counted only once.

In equilibrium, $\nu_\beta(0)$, j_β and K_{mn} all vanish identically, and hence $I_{\alpha\beta} = 0$. Our representation makes the "violation" of the Einstein or Green-Kubo in a NESS apparent and provides a physically transparent expression for the difference between dispersions and mobilities.

Molecular motor.—As an illustration of the general framework we consider any discrete state model of a molecular motor. A transition from state m to state n may either advance the motor a spatial distance $d_{mn} = -d_{nm}$, or be associated with a chemical reaction of the type $\sum_\alpha r^\alpha_{mn} A_\alpha \to \sum_\alpha s^\alpha_{mn} A_\alpha$, or contain both. The index $\alpha = t$, d, p labels the chemical species ATP, ADP, and P_i, respectively, and r^α_{mn} and $s^\alpha_{mn} (= r^\alpha_{nm})$ are the corresponding stoichiometric factors for the forward and backward reaction. For each transition and each species a "chemical distance"

$$d^\alpha_{mn} \equiv r^\alpha_{mn} - s^\alpha_{mn} = r^\alpha_{mn} - r^\alpha_{nm} = -d^\alpha_{nm}, \tag{15}$$

denotes the number of consumed (or, if negative, produced) molecules of type α. The chemical species are provided at externally controlled concentrations c_α. For any motor and no applied external force ($f = 0$) there are concentrations c^{eq}_α at which the motor is in equilibrium with its thermal and chemical environment. Assuming ideal behavior, the concentrations are linked to the chemical potentials by $\mu_\alpha = \mu^{\text{eq}}_\alpha + T \ln c_\alpha / c^{\text{eq}}_\alpha$. If, still at $f = 0$, the chemical potentials deviate from their equilibrium value, the transition rates are modified according to the usual mass action law kinetics,

$$w_{mn} = w_{mn}^{\mathrm{eq}} \exp\sum_{\alpha} \Delta\mu_\alpha r_{mn}^\alpha / T, \tag{16}$$

where $\Delta\mu_\alpha \equiv \mu_\alpha - \mu_\alpha^{\mathrm{eq}}$. Note that the dependence of these rates on the chemical potentials ($h_\alpha = \Delta\mu_\alpha$) obeys (3) which justifies *a posteriori* to denote the stoichiometric coefficients by r_{mn}^α. We make no particular assumptions on the force dependence of the individual transition rates but require that the ratio between forward and backward rates obeys, as usually assumed, the LDB condition

$$\frac{w_{mn}(f)}{w_{nm}(f)} = \frac{w_{mn}(0)}{w_{nm}(0)} \exp(f d_{mn}/T). \tag{17}$$

Hence, the sensitivities $r_{mn} \equiv T\partial_f \ln w_{mn}$ obey the relation (3).

For a simple but still instructive specific example, we consider a "one-state" ratchet model where the forward rate (driven by ATP hydrolysis) and the backward rate (synthesizing ATP from ADP and P_i) are given by

$$w_+ = w_+^{\mathrm{eq}} \exp[(\Delta\mu^t + f\theta_+ d)/T] \tag{18}$$

and

$$w_- = w_-^{\mathrm{eq}} \exp[(\Delta\mu^d + \Delta\mu^p - f\theta_- d)/T], \tag{19}$$

respectively. The load sharing factors θ_+ and θ_- with $\theta_+ + \theta_- = 1$ guaranteeing the LDB condition (3) are related to the distance of the activation barrier in forward and backward direction, respectively [12].

Since in this model all sites are physically equivalent but only spatially translated a distance d, there are no current correlations, so that only the local terms contribute. With $j = d(w_+ - w_-)$, the ordinary spatial mobility becomes $\mu \equiv \partial_f j = d^2[\theta_+ w_+ + \theta_- w_-]/T$, and the corresponding diffusion coefficient $D = (1/2)d^2[w_+ + w_-]$. The difference $I = -d^2(w_+ - w_-)(\theta_+ - \theta_-)/2$ vanishes not only in equilibrium ($w_+ = w_-$) but even in a NESS for a symmetric barrier ($\theta_+ = \theta_- = 1/2$).

Expressed in terms of an effective temperature,

$$T^{\mathrm{eff}} \equiv D/\mu = T + I/\mu = \frac{T(\rho + 1)}{2(\theta_+\rho + 1 - \theta_+)}, \tag{20}$$

where $\rho \equiv w_+/w_-$, one sees that for $0 \leq \theta_+ \leq 1$, T^{eff}/T can acquire any value $\geq 1/2$. If we allow the somewhat more extreme structural choice of $\theta_+ > 1$ (thus assuming that both forward and backward steps are promoted with increasing force) then even negative values of the effective temperature become possible. Clearly, even this simple example demonstrates that the idea of phenomenologically characterizing active processes by an elevated "effective temperature" is not really consistent. It rather conceals the physically transparent additive relationship between mobility and dispersion by replacing it with a multiplicative factor.

Rather than looking at the response of the motor to a changing applied force, one can ask for the response to a change in concentration of ATP or ADP, i.e., to a change in the chemical potential with $h_\beta \equiv \mu_\beta$. For the current, we can either choose the ordinary spatial current $j(t)$ or the current of consumed α molecules $j_\alpha(t)$. How the corresponding mean currents change with the chemical potential of β molecules is expressed by the mobility tensor $\kappa_{\alpha\beta}$ shown in Table I which includes the "cross" mobilities between chemical and mechanical (here denoted by an index f) distances and fields. We refrain from listing the dispersions, which are in this case symmetrical with $D_{\alpha\beta} = D_{\beta\alpha}$, and the corresponding effective temperatures $T_{\alpha\beta}^{\mathrm{eff}}$ except for pointing out that the latter are asymmetric and depend on the choice of indices even for fixed rates.

TABLE I. Generalized mobilities for the one-state motor.

$T\kappa_{\alpha\beta}$	β	f	t	d
α				
f		$d^2(\theta_+ w_+ + \theta_- w_-)$	dw_+	$-dw_-$
t		$d(\theta_+ w_+ + \theta_- w_-)$	w_+	$-w_-$
d		$-d(\theta_+ w_+ + \theta_- w_-)$	$-w_+$	w_-

While the evaluation of mobilities and dispersions is straightforward also for any more complex specific model as will be illustrated elsewhere, a few universal statements seem to be possible beyond the obvious ones referring to equilibrium. As one example consider the observation made in [11] for a particular two state motor model that at stalling conditions, $j = 0$ at $f = f_s$, the usual Einstein relation between mobility and diffusion constant holds true, even though idle chemical currents dissipate energy. Our expressions (6), (13), and (14) show that, in general, the validity of the Einstein relation requires not only that $j = 0$ but moreover that any link carrying a nonzero probability current K_{mn} be not sensitive to the force f, i.e., for any $K_{mn} \neq 0$, $r_{mn} = r_{nm} = 0$ must hold. The latter condition will not necessarily be met at stalling since even pure chemical transitions with $d_{mn} = 0$ will, in general, be affected by changing the applied force.

Proof of (11).—In the differential mobility

$$\kappa_{\alpha\beta} \equiv \partial_{h_\beta} j_\alpha = \sum_{mn} d_{mn}^\alpha \partial_{h_\beta}(p_m w_{mn}) \tag{21}$$

$$= \sum_{mn} d_{mn}^\alpha (\partial_{h_\beta} p_m) w_{mn} + \kappa_{\alpha\beta}^{\mathrm{loc}} \tag{22}$$

the term $\partial_{h_\beta} p_m \equiv \partial_{h_\beta}\langle\delta_{n(t)m}\rangle$ must be expressed by a correlation function. In [6] we have determined the response of an observable at time t_2 to a deltalike perturbation at time t_1. Specialized to the present quantities and slightly adapting the notation, this relation reads

$$\left.\frac{\delta\langle\delta_{n(t_2)m}\rangle}{\delta h_\beta(t_1)}\right|_{\{h_\beta\}=\mathrm{const}} = \langle\delta_{n(t_2)m} B(t_1)\rangle, \tag{23}$$

where the conjugate variable $B(t_1)$ is given by

$$TB(t_1) \equiv \sum_j \delta(t_1 - t_j) r^{\beta}_{n_j^- n_j^+} - \sum_k w_{n(t_1)k} r^{\beta}_{n(t_1)k} \tag{24}$$

$$= j_{\beta}(t_1) + \sum_j \delta(t_1 - t_j) r^{\beta}_{n_j^+ n_j^-} - \sum_k w_{n(t_1)k} r^{\beta}_{n(t_1)k}, \tag{25}$$

where we have used (1) and (3). If the correlation function $\langle \delta_{n(t_2)m} \sum_j \delta(t_1 - t_j) r^{\beta}_{n_j^+ n_j^-} \rangle$ is averaged over the states n_j^- before the jump at t_1 one gets

$$\left\langle \delta_{n(t_2)m} \sum_j \delta(t_1 - t_j) r^{\beta}_{n_j^+ n_j^-} \right\rangle \tag{26}$$

$$= \left\langle \delta_{n(t_2)m} \sum_k p_k w_{kn(t_1)} r^{\beta}_{n(t_1)k} / p_{n(t_1)} \right\rangle. \tag{27}$$

Putting together (23)–(27) and using (6), we can write

$$T \frac{\delta \langle \delta_{n(t_2)m} \rangle}{\delta h_{\beta}(t_1)} \bigg|_{\{h_{\beta}\}=\mathrm{const}} = \langle \delta_{n(t_2)m} [j_{\beta}(t_1) - \nu_{\beta}(t_1)] \rangle. \tag{28}$$

Thus the response of the current at the later time, $j_{\alpha}(t_2) = \sum_{nl} \delta_{n(t_2)n} d^{\alpha}_{nl} w_{nl}$, to a deltalike perturbation at the earlier time can be expressed as

$$T \frac{\delta \langle j_{\alpha}(t_2) \rangle}{\delta h_{\beta}(t_1)} \bigg|_{\{h_{\beta}\}=\mathrm{const}} = \langle j_{\alpha}(t_2) [j_{\beta}(t_1) - \nu_{\beta}(t_1)] \rangle. \tag{29}$$

Integrating over the time-difference $t_2 - t_1$, we obtain our main result (11).

Concluding perspective.—We have expressed the generalized mobilities by current correlation functions for any driven system described by a master equation with transition rates which obey a local detailed balance condition as it should hold for transport in a well-defined thermal environment. Without this condition one could still express the mobility by an integral over some correlation function as a minor modification of our proof would show. The physically transparent connection to the dispersions emphasized here, however, would then be lost. Even though our relation is remarkably reminiscent of the well-known linear response result, a crucial difference should not go unnoticed. For a nonequilibrium steady state as investigated here, the relevant correlations involve a "sensitivity-weighted" current. As an observable, the latter requires knowledge of how the rates depend on the external perturbation. While this is not an issue in any theoretical modeling, it will limit the direct application to those experimental systems for which this property of the rates is accessible. In the familiar linear response realm of the regular Green-Kubo relations, such explicit knowledge is not necessary. This observation might support the view that often the quantitative evaluation of exact nonequilibrium relations requires more specific input than their equilibrium counterparts do.

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