Generalized fluctuation-dissipation and reciprocal relations for Brownian sieves and molecular machines

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A Brownian sieve is a spatially periodic microstructured device that combines the effects of thermal noise, local spatial asymmetry, and external forces to separate particles based on their transport properties. By treating the motion of an individual particle as a cyclical process in which the particle fluctuates away from and returns to the origin of some unit cell, I derive generalized fluctuation-dissipation and reciprocal relations for the averages (and for all moments) of the number of periodic displacements that are exact and valid for arbitrary values of the external forces. These relations hold not only for Brownian sieves, but for all molecular machines in which a nanoscale system couples two chemical, mechanical, or transport processes by a cycle in which the molecular machine itself fluctuates away from and then returns to some arbitrary reference state, in the process doing or receiving work on or from the environment.

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Brownian sieves are two-dimensional filters with tiny obstacles that form a periodic maze through which particles or molecules [1–6] move. Under the action of external forces, the distances traveled by any particle in the two spatial directions in any time period depend differently on the diffusion coefficient and on the mobility of the particle so that over time different type particles in a mixture become separated in space. The basis of the separation is the Brownian motor effect in which three ingredients, (1) Brownian motion due to thermal (or other) noise; (2) local asymmetry in the environment; and (3) input energy from external forces [7–9] or local temperature gradients [10], combine to give rise to directed motion over macroscopic length scales.

Consider the two microstructured sieves shown schematically in Figs. 1(a) and 1(b). These sieves are periodic (with periods l_x and l_y) and couple flows in the x (y) directions to forces in the y (x) direction. In the absence of external forces, a particle executes an unbiased random walk. Starting with a particle at the origin, any specific trajectory in which the particle moves from (0, 0) at $t=0$ to $(+il_x,-jl_y)$ at $t=t^*$ via the path $(x(t),y(t))$ [one such trajectory is shown as solid curves in Figs. 1(a) and 1(b)] is exactly as likely as the microscopic reverse trajectory that takes the particle from (0, 0) at $t=0$ to $(-il_x,+jl_y)$ at $t=t^*$ via the path $(x(t^*-t)-l_x,y(t^*-t)+l_y)$ [shown as dotted curves in Figs. 1(a) and 1(b)]. Thus, irrespective of the structure of the sieve and of the strength of Brownian motion, the long time averages of the number of periods traveled in the x and y directions are, in the absence of external forces, zero, $\langle i\rangle=0$ and $\langle j\rangle=0$, although the diffusion will not in general be circularly symmetric, i.e., $\langle ij\rangle\neq 0$. For example, in Fig. 1(a), the diffusion will be greater along the diagonal between the upper left and lower right corners than along the diagonal between the upper right and lower left corners. In the limit that the obstacles are very close together, the motion of particles will be approximately one dimensional (1D) (along the diagonal), but not unidirectional.

External forces break the symmetry between forward and microscopically reversed trajectories that disallows directed motion. The energy provided by the external force, in combination with spatial symmetry breaking and with Brownian motion, allow coupled transport in two–dimensional Brownian sieves by which particles having different physical properties can be separated. In the devices shown in Figs. 1(a) and 1(b), thermal noise is essential to allow a force in the y direction to drive motion in the x direction.

Onsager [11] showed that for sufficiently small forces the cross-coupling coefficients in an expansion of the velocities in powers of the forces are equal. This reciprocity between the velocities and forces does not hold for larger forces where higher order terms become important. Further, under some circumstances, as, e.g., in the device shown in Fig.

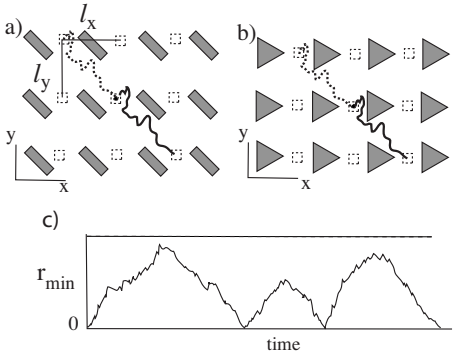

FIG. 1. (a) and (b) Two idealized Brownian sieves with very different symmetry properties. The small boxes indicate periodically related points that we arbitrarily choose as the origins of the unit cells of the lattice. In (a) symmetry is broken in both the x and y directions: there are no x,z *or* y,z planes about which there is reflection symmetry. In (b) symmetry is broken in the x direction: there is no reflection symmetry about any y,z plane, but there is reflection symmetry about an x,z plane. Two symmetry-related trajectories are illustrated for each device—a "forward" trajectory (solid line), and a microscopic reverse trajectory (dotted line). (c) Plots of the distance between a particle and the closest origin of a unit cell for some trajectory as a function of time.

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1(b), the linear cross-coupling coefficients are zero by symmetry [2,12]. The flows are coupled at higher order [2,12], but no general relationship describing the cross coupling has been given even for very small forces.

Here, instead of focusing on the velocities I treat the motion as a cyclical process in which a particle, starting at the origin of some unit cell of a periodic structure, fluctuates away from and then returns to the origin of some unit cell, as shown in Fig. 1(c), where we plot the fluctuating distance $r_{\min}$ between the particle and the nearest origin of a unit cell. The focus on completions of forward and reverse cycles of fluctuation from and regression to periodically related conditions is reminiscent of the approach developed by Hill [13,14] for analyzing biological energy transduction in terms of the cycles of the proteins responsible for these energy conversion processes, and has been used to derive nonlinear reciprocal relations for molecular motors [15], and coupled electron transport through mesoscopic devices [16].

In each cycle of excursion from and return to periodically related points, the particle will have moved some number of periods, i, in the horizontal direction, and some number of periods, j, in the vertical direction, having done (recieved) work on (from) the sources of the external forces $W_{\text{ext}}=-il_xF_x-jl_yF_y$. For each trajectory in which the particle moves i periods horizontally and j periods vertically, there is a microscopic reverse trajectory in which the particle travels $-i$ periods horizontally and $-j$ periods vertically. The ratio of the overall probabilities for trajectories that travel i and j periods to those that travel $-i$ and $-j$ periods is

$$\frac{P_{i,j}}{P_{-i,-j}} = e^{-(i\tilde{F}_x+j\tilde{F}_y)}, \tag{1}$$

where $\tilde{F}_x=l_xF_x/(k_BT)$ and $\tilde{F}_y=l_yF_y/(k_BT)$ and k_BT is the product of Boltzmann's constant and the Kelvin temperature. Equation (1) follows from the principle of microscopic reversibility. Note that the ratio $P_{i,j}/P_{-i,j}$ is not thermodynamically constrained since a trajectory in which a particle moves $-i$ and $+j$ periods is not the microscopic reverse of any trajectory in which the particle moves $+i$ and $+j$ periods. Indeed, it is this ratio that is the key quantitative measure of the strength of coupling between the motion in the horizontal (vertical) direction and the forces in the vertical (horizontal) direction.

The statistical moments for the number of periods traveled during each excursion away from and return to the origin of a unit cell can be calculated from the averages

$$\langle i^n j^m\rangle = \sum_{i,j=-\infty}^{+\infty} i^n j^m P_{i,j} \tag{2}$$

for all m and n. Equation (1) can be used to rewrite the averages in Eq. (2) as

$$\langle i^n j^m\rangle = \sum_{i,j=1}^{+\infty} i^n j^m\{\delta_m P_{i,0}\phi_{i,0}^{(m+n)} + \delta_n P_{0,j}\phi_{0,j}^{(m+n)} + [P_{i,j}\phi_{i,j}^{(m+n)} + (-1)^n P_{-i,j}\phi_{-i,j}^{(m+n)}]\}, \tag{3}$$

where $\phi_{i,j}^{(m+n)}=1+(-1)^{m+n}e^{(i\tilde{F}_x+j\tilde{F}_y)}$, and where the Kroneker delta δ_α for any argument α is one if $\alpha=0$ and zero otherwise. The sums in Eq. (3) now run over only positive integers i and j. The $\phi_{i,j}^{(m+n)}$ contain all of the thermodynamic dependence of the transport on the forces, while the $P_{i,j}$ contain the dependence of the transport coefficients on the forces due to kinetic or structural factors. Expanding the $\phi_{i,j}^{(m+n)}$ on the right-hand side of Eq. (3) in powers of $\tilde{F}_x$ and $\tilde{F}_y$ we have

$$\langle i^n j^m\rangle = \mathcal{D}^{(n,m)} + \sum_{k,l=0}^{\infty}(1-\delta_k\delta_l)G_{k,l}^{(n,m)}\frac{\tilde{F}_x^k\tilde{F}_y^l}{k!l!}, \tag{4}$$

where $\mathcal{D}^{(n,m)}=[1+(-1)^{n+m}]G_{0,0}^{(n,m)}$ is a diffusion function, and the coefficient functions are

$$G_{k,l}^{(n,m)} = \pm\sum_{i,j=1}^{+\infty} i^{n+k}j^{m+l}[\delta_{m+l}P_{i,0} + \delta_{n+k}P_{0,j} + (P_{i,j} \pm P_{-i,j})]. \tag{5}$$

We take $+$ for the first $\pm$ in Eq. (5) when $n+k+m+l$ is an even integer and $-$ when $n+k+m+l$ is an odd integer, and we take $+$ for the second $\pm$ in Eq. (5) when $n+k$ is an even integer, and $-$ when $n+k$ is an odd integer. The coefficient functions obey the symmetry relations

$$G_{k,l}^{(n,m)} = G_{k-\alpha,l-\beta}^{(n+\alpha,m+\beta)}, \tag{6}$$

where α and β are any integers consistent with the constraint that all indices must be greater than or equal zero in any expression. Equation (6) is an exact relation that follows deductively from Eq. (1).

Because the kinetic factors $G_{k,l}^{(n,m)}$ are functions of $\tilde{F}_x$ and $\tilde{F}_y$ it is difficult to directly use the symmetry relation for interpreting experiments since it is impossible to separate the dependencies of the averages $\langle i^n j^m\rangle$ on $\tilde{F}_x$ and $\tilde{F}_y$ due to the kinetic factors $G_{k,l}^{(n,m)}$ from the dependencies arising from the thermodynamic factors $\phi_{i,j}^{(n,m)}$. However, the $G_{k,l}^{(n,m)}$ themselves can be expanded in powers of $\tilde{F}_x$ and $\tilde{F}_y$,

$$G_{k,l}^{(n,m)} = \sum_{r,s=0}^{\infty} g_{k,l;r,s}^{(n,m)}\tilde{F}_x^r\tilde{F}_y^s, \tag{7}$$

where the $g_{k,l;r,s}^{(n,m)}$ are constant ($\tilde{F}_x$ and $\tilde{F}_y$ independent) coefficients. From Eq. (6) we have the equalities

$$g_{k,l;r,s}^{(n,m)} = g_{k-\alpha,l-\beta;r,s}^{(n+\alpha,l+\beta)} \tag{8}$$

for all integers α and β subject to the constraint that all indices are greater than or equal zero. By inserting Eq. (8) into Eq. (4) and focusing on terms of different total order $p=k+l+r+s$ with respect to the sum of the powers to which $\tilde{F}_x$ and $\tilde{F}_y$ are raised we find

$$\langle i^n j^m\rangle = \sum_{p=0}^{\infty}\sum_{q=0}^{p}(2D_{q,p-q}^{(n,m)} + L_{q,p-q}^{(n,m)})\frac{\tilde{F}_x^q\tilde{F}_y^{p-q}}{q!(p-q)!}, \tag{9}$$

where the coefficients are

$$D_{a,b}^{(n,m)} = \frac{[1+(-1)^{n+m}]}{2}g_{0,0;a,b}^{(n,m)},$$

$$L_{a,b}^{(n,m)} = \sum_{k=0}^{a} \sum_{l=0}^{b} (1 - \delta_k \delta_l) g_{k,l;a-k,b-l}^{(n,m)}. \tag{10}$$

The indices a and b are any non-negative integers. Using the symmetry relation Eq. (8) we find by induction the general reciprocal relations

$$L_{1,0}^{(n,m)} = L_{0,1}^{(n+1,m-1)}, \quad n \geqslant 0, \quad m \geqslant 1, \tag{11}$$

and the general fluctuation-dissipation relation by which the coefficients of the pth-order term in the expression of the odd cumulants can be written in terms of the coefficients of the $(p-1)$st-order terms in the expressions for the even cumulants

$$L_{a,0}^{(n,m)} = L_{a-1,0}^{(n+1,m)} + D_{a-1,0}^{(n+1,m)},$$

$$L_{0,b}^{(n,m)} = L_{0,b-1}^{(n,m+1)} + D_{0,b-1}^{(n,m+1)},$$

$$L_{a,b}^{(n,m)} = L_{a,b-1}^{(n,m+1)} + D_{a,b-1}^{(n,m+1)} + D_{a-1,b}^{(n+1,m)}$$
$$\text{for } n+m = \text{odd}, \ a,b > 0. \tag{12}$$

All coefficients are independent of $\tilde{F}_x$ and $\tilde{F}_y$ and are dimensionless since we have focused not on velocities (or periods traveled per unit time) but on the number of spatial periods travelled per cycle of fluctuation of a particle away from and regression to the origin of a unit cell. Unlike the Stokes-Einstein fluctuation dissipation relation and the Onsager reciprocal relation for the coefficients in expressions for velocities or fluxes (i.e., for number of events normalized by time), the relations in Eqs. (11) and (12), derived for the number of periods travelled during a cycle of fluctuation away from and return to origins of unit cells, are exact. The higher-order relations contained in Eq. (12) can be used to build up the expressions for the averages and cumulants to arbitrary order.

To illustrate how these generalized fluctuation-dissipation and reciprocal relations can be used experimentally we write explicitly the equations for the averages $\langle i \rangle$ and $\langle j \rangle$ through second order:

$$\langle i \rangle = L_x \tilde{F}_x + L_c \tilde{F}_y + Q_x \tilde{F}_x^2 + (M + C) \tilde{F}_x \tilde{F}_y + M^* \tilde{F}_y^2 + \cdots,$$

$$\langle j \rangle = L_y \tilde{F}_y + L_c \tilde{F}_x + Q_y \tilde{F}_y^2 + (M^* + C^*) \tilde{F}_x \tilde{F}_y + M \tilde{F}_x^2 + \cdots. \tag{13}$$

From Eqs. (11) and (12) we have the first-order relations

$$L_x = L_{1,0}^{(1,0)} = D_{0,0}^{(2,0)},$$

$$L_y = L_{0,1}^{(1,0)} = D_{0,0}^{(0,2)},$$

$$L_c = L_{0,1}^{(1,0)} = L_{1,0}^{(0,1)} = D_{0,0}^{(1,1)}. \tag{14}$$

The second-order terms are $Q_x = L_{2,0}^{(1,0)}$ and $Q_y = L_{0,2}^{(0,1)}$, and using the symmetry relation Eq. (8) we find

$$M = g_{1,1;0,0}^{(1,0)} + g_{0,1;1,0}^{(1,0)} = g_{2,0;0,0}^{(0,1)} + g_{1,0;1,0}^{(0,1)} = L_{2,0}^{(0,1)},$$

$$M^* = g_{0,2;0,0}^{(1,0)} + g_{0,1;0,1}^{(1,0)} = g_{1,1;0,0}^{(0,1)} + g_{1,0;0,1}^{(0,1)} = L_{0,2}^{(1,0)},$$

$$C = g_{0,1;1,0}^{(1,0)} = D_{1,0}^{(0,2)},$$

$$C^* = g_{1,0;0,1}^{(1,0)} = D_{0,1}^{(2,0)}. \tag{15}$$

The linear relations are particularly experimentally useful since the reciprocal relation $L_{0,1}^{(1,0)} = L_{1,0}^{(0,1)}$ reduces the number of coefficients to first order for the averages from four to three, and the fluctuation-dissipation relations allow these three coefficients to be determined by measuring the cumulants in the absence of forces. The second-order relations are also very important experimentally—for some devices such as that shown in Fig. 1(b) the linear coupling coefficient $L_{0,1}^{(1,0)} = L_{1,0}^{(0,1)} = L_c$ is identically zero by symmetry, and the lowest-order coupling is at second order. In this case, either M or M^* or both are zero depending on whether there is reflection symmetry about the y axis, about the x axis, or about both axes, respectively. The higher-order relations contained in Eq. (11) along with Eq. (9) can be used to build up the expressions for the averages and cumulants to arbitrary order, but these are experimentally less relevant.

If the obstacles are very close together, we can reasonably approximate that during each cycle of fluctuation away from and return to an origin of a unit cell i and j take on only the values $i = -1, 0, +1$ and $j = -1, 0, +1$. For this case we can truncate the sum in Eq. (3) and all coefficients in the expansion in powers of $\tilde{F}_x$ and $\tilde{F}_y$ can be written in terms of $P_{1,0}, P_{0,1}$, and the sum $(P_{1,1} + P_{-1,1} \equiv A)$ and difference $(P_{1,1} - P_{-1,1} \equiv B)$ to find the simple closed equations for the moments $\langle i^n j^m \rangle$,

$$\langle i^n j^m \rangle = \delta_m P_{1,0}[1 + (-1)^n e^{\tilde{F}_x}] + \delta_n P_{0,1}[1 + (-1)^m e^{\tilde{F}_y}]$$
$$+ A \pm e^{-\tilde{F}_y}[A \cosh(\tilde{F}_x) - B \sinh(\tilde{F}_x)], \quad n \text{ even},$$

$$\langle i^n j^m \rangle = \delta_m P_{1,0}[1 + (-1)^n e^{\tilde{F}_x}] + \delta_n P_{0,1}[1 + (-1)^m e^{\tilde{F}_y}]$$
$$+ B \mp e^{-\tilde{F}_y}[B \cosh(\tilde{F}_x) - A \sinh(\tilde{F}_x)], \quad n \text{ odd}, \tag{16}$$

where we take the top symbol in the $\pm$ and $\mp$ in each equation when m is even, and the bottom symbol when m is odd. The probabilities $P_{1,1}$, $P_{-1,1}$, $P_{1,0}$, and $P_{0,1}$ parametrize all kinetic dependence of the transport on the external forces, while the explicit functions of $\tilde{F}_x$ and $\tilde{F}_y$ capture all thermodynamic dependence of the transport on the external forces.

The derivation of the generalized reciprocal relation Eq. (11) and the generalized fluctuation-dissipation relations Eq. (12) is based on treating the motion of an individual particle as a cyclical process in which the particle fluctuates away from, and then returns to the origin of a unit cell in a spatially periodic system, and where particle-particle interactions are ignored. The predictions can be directly tested experimentally using single particle tracking techniques. All results follow deductively from Eq. (1) for the probabilities of discrete events normalized by the number of cycles of fluctuation away from and return to some reference state (the origin of a unit cell here).

Other work on deriving nonlinear response coefficients has focused on the coefficients of the currents [17,18] based

on "fluctuation theorems" [19]. We can make contact with that work using the Onsager-Machlup [24] thermodynamic action approach for irreversible thermodynamics. This will further allow us to express the generalized fluctuation-dissipation relations derived here in the context of ensemble experimental measures of the performance of Brownian sieve devices, and also to cast our results in a form more amenable to use in interpreting experiments on electron conduction through periodic arrays of quantum antidots [20] and other mesoscopic conductors [21,22], possibly in the presence of magnetic fields [23].

The Langevin equation for motion of a single particle is

$$m\mathbf{a} + \gamma\mathbf{v} - \mathbf{F} = \sqrt{2\gamma}\boldsymbol{\epsilon}(t), \tag{17}$$

where $\boldsymbol{\epsilon}(t)$ is Gaussian white noise, γ is the coefficient of viscous friction, and we work in units where $k_BT=1$. For charged particles moving on a lattice in the presence of external electric and magnetic fields the force (ignoring particle-particle interactions) can be written $\mathbf{F}=-\boldsymbol{\nabla}U+q(\mathbf{E}+\mathbf{v}\times\mathbf{B})$. The effect of the "obstacles" in a Brownian sieve is described by the gradient force $-\boldsymbol{\nabla}U$ and the effect of the external electric field is given by the electric force $q\mathbf{E}$ and the Lorentz force in the presence of a magnetic field is $q(\mathbf{v}\times\mathbf{B})$.

For an overdamped system the inertial term ($m\mathbf{a}$) is negligible. Thus, following Onsager and Machlup [24], we use the fact that the probability for any sequence of "Brownian kicks" over a period t^* can be written $P[\boldsymbol{\epsilon}(t)]=\exp[-1/2\int_0^{t^*}dt\,\boldsymbol{\epsilon}^2(t)]$ to write the conditional probability for a trajectory of a particle as [25,26]

$$P[\mathbf{r}(t)|B] = J(\mathbf{r})\exp\left[-\frac{1}{2}\int_0^{t^*}dt\left(\frac{\gamma\mathbf{v}-[-\boldsymbol{\nabla}U+q(\mathbf{E}+\mathbf{v}\times\mathbf{B})]}{\sqrt{2\gamma}}\right)^2\right], \tag{18}$$

where the position vector is $\mathbf{r}(t)=\{x(t),y(t)\}$ in Cartesian coordinates. We interpret the squaring operation as a dot product and $J(\mathbf{r})=d\boldsymbol{\epsilon}/d\mathbf{r}$ is the Jacobian matrix by which we transform from a trajectory in noise space $[\boldsymbol{\epsilon}(t)]$ to a trajectory in position space $[\mathbf{r}(t)]$. The conditional probability for a reverse trajectory $P[\mathbf{r}(t^*-t)]$ can be calculated exactly as in Eq. (18) but with $\mathbf{v}\to-\mathbf{v}$ and $B\to-B$. As Bier *et al.* [25] pointed out, the ratio between the conditional probability for any trajectory $[\mathbf{r}(t)]$ and its reverse $[\mathbf{r}(t^*-t)]$ is thus time and path independent,

$$\frac{P[\mathbf{r}(t)|B]}{P[\mathbf{r}(t^*-t)|-B]} = \exp\left(-\int_0^{t^*}ds\,\mathbf{v}(t)\cdot(q\mathbf{E}-\boldsymbol{\nabla}U)\right) = e^{(W_{\text{ext}}+\Delta U)}, \tag{19}$$

where $\int_0^{t^*}dt\,\mathbf{v}\cdot(q\mathbf{E}-\boldsymbol{\nabla}U)$ is the integrated "force×distance" work done by (on) the combined external and internal fields in the forward trajectory and $\Delta U=U[\mathbf{r}(0)]-U[\mathbf{r}(t^*)]$.

Equation (19) is a special case of the generalized fluctuation-dissipation theorem of Bochkov and Kuzovlev [27] that relates a trajectory and its time reverse to the change in internal energy due to the trajectory. Equations of this form have come to be known as "fluctuation theorems" [28,29].

For trajectories with periodically related end points $\int_0^{t^*}dt\,\mathbf{v}\cdot\boldsymbol{\nabla}U=0$ and hence

$$\frac{\tilde{P}_{i,j}(t^*)}{\tilde{P}_{-i,-j}(t^*)} = e^{-q(il_xE_x+jl_yE_y)}, \tag{20}$$

where $\tilde{P}_{i,j}(t^*)=P[\{x+il_x,y+jl_y\},t^*|\{x,y\},0]$ is the probability density, given that a particle starts in the region $\{x\pm dx,y\pm dy\}$, that the particle is in the region $\{x+il_x\pm dx,y+jl_y\pm dy\}$ some time t^* later. In terms of experiment, if we place a large number of noninteracting particles N_T in the unit cell about the origin of a device such as those shown in Fig. 1 and allow the particles to drift and diffuse for a time t^* and then count the number of particles in each unit cell of the device, the results are directly related to the probabilities in Eq. (16), i.e., $P_{i,j}/P_{-i,-j}=N_{i,j}/N_{-i,-j}$ if the measurement time is long enough that on average a particle makes many (>100) cyclic excursions away from and return to a unit cell. The derivation of the generalized fluctuation-dissipation relations Eqs. (11) and (12) from the averages and moments of the position of the particles (as observed experimentally), given by $\langle x^ny^m\rangle=l_x^nl_y^m\Sigma_{i,j}i^nj^mN_{i,j}/N_T$, follows exactly as shown in Eqs. (2)–(10) with the only difference being that the coefficients thus derived, with $N_{i,j}/N_T$ inserted for $P_{i,j}$ in Eqs. (2), (3), and (5), depend on the measurement time t^*. However, the time dependence is such that the equalities in Eqs. (11) and (12) hold for all t^* and thus the velocities and cumulants can be written as

$$\langle v_x^nv_y^m\rangle = \frac{l_x^nl_y^m}{\langle\tau\rangle}\langle i^nj^m\rangle, \tag{21}$$

where $\langle\tau\rangle=\Sigma_{i,j=-\infty}^{+\infty}\tau_{i,j}P_{i,j}$ is the average time for a cycle away from and return to the origin of a unit cell, and $\tau_{i,j}$ are the individual cycle times. The expression for the average cycle time can be simplified by the identity $\tau_{i,j}=\tau_{-i,-j}$ that follows from the direction independence of the last touch–first touch times between any two points proven by Bier *et al.* [25].

A particularly salient example of the importance of the nonlinear relations arises from consideration of the behavior of particles in the device shown in Fig. 1(b). If we place a large number of particles in one unit cell of this device and allow them to diffuse in the absence of external forces particles will spread out symmetrically such that $\langle ij\rangle=0$. From the linear relations $L_c=0$ we would predict there to be no coupled transport. However, if the experiment is repeated, but with $\tilde{F}_y\neq0$ a net drift to the right (in the positive x direction) would in fact be observed. Further, if the field is inverted, $\tilde{F}_y\to-\tilde{F}_y$, the drift is still to the right [12]. Thus to lowest order the coupled transport [right (left) motion coupled driven by an up (down) force] is quadratic in $\tilde{F}_y$ and $\langle v_x\rangle=l_xM\tilde{F}_y^2/\langle\tau\rangle$ so $M\neq0$. Note that a force in the x direction $\tilde{F}_x$ does not lead to directed motion in the y direction and so we have $M^*=0$.

Although I have derived the extended symmetry relations, Eqs. (6) and (8), the generalized reciprocal relation, Eq. (11),

and the generalized fluctuation-dissipation relations, Eqs. (12), for the very specific case of particles undergoing diffusion and drift on a periodic lattice of obstacles, the basic approach is much more general and pertains to a wide variety of coupled transport processes that can be described in terms of discrete events, including coupled chemical reactions, biological transport processes such as active transport[30], coupled transport across membranes, and molecular motors [31], where the protein that mediates the transport is the fluctuating mesoscopic region. Consider for example a biomolecular motor that steps along a polar polymeric track (with ends labeled + and −) and catalyzes conversion between a fuel molecule [adenosine triphosphate, (ATP)] and a waste molecule [adenosine diphosphate (ADP)]. Let the protein start in some arbitrary reference conformation. Because of thermal noise the protein will certainly fluctuate away from this conformation, and eventually return, in what is often termed a catalytic cycle. During this cycle of fluctuation and regression the protein will have made some number i (possibly zero) steps of length l_x against an external force F_{ext} along its polymeric track and will have catalyzed conversion between some number j (possibly zero) of ATP and ADP. With $\tilde{F}_x = F_{\text{ext}} l_x / k_B T$ and $\tilde{F}_y = \Delta\mu_{\text{ATP}} / k_B T$, Eq. (2) expresses the relationship between the probability in one recursion cycle of the protein to convert j molecules of ATP to ADP while taking i steps toward the + end of the track to the probability to convert j molecules of ADP to ATP while taking i steps to the − end of the track. Derivation of the extended symmetry relations and fluctuation-dissipation relations for the averages $\langle i \rangle$ and $\langle j \rangle$ and the cumulants $\langle i^2 \rangle$, $\langle j^2 \rangle$, and $\langle ij \rangle$ proceeds exactly as described from Eq. (3) to Eq. (12). The example of a molecular motor is particularly timely since recent experiments allow the direct observation of molecular motor stepping [33], and much effort is being devoted to develop techniques that will allow observation of individual events of ATP hydrolysis in single-molecule experiments [34]. Simultaneous measurement of chemical and mechanical events is tantamount to determining the full counting statistics [32] for molecular motors and can be used for direct comparison with the symmetry relations given here by determining the ratio of the average number of steps taken to the average number of chemical conversions between ATP and ADP in any time interval at different values of the applied force. Now that experiments measuring discrete processes—transfer of individual charges [32], single steps along a polymer lattice [33], and single chemical conversions between a substrate and product pair by an enzyme [34]—are routinely accomplished we can focus on the differences and ratios between the numbers of these elementary events in a recursion cycle of the molecular machine to see that deep symmetry relations hold even far from thermodynamic equilibrium.

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