Master equation approach to molecular motors

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A master equation approach to molecular motors allows us to describe a mechanochemical cyclic system where chemical and translational degrees of freedom are treated on an equal footing. A generalized detailed balance condition in the out-of-equilibrium regime is shown to be compatible with the Fokker-Planck equation in the continuum limit. The Onsager reciprocity relations hold for stationary states close to equilibrium, provided the generalized detailed balance condition is satisfied. Semiphenomenological considerations in the case of motor proteins lead to a discrete kinetics model, for which interesting observable quantities may be directly calculated and compared with experimental data.

Current models used to describe the properties of molecular motors and the energy transduction process fall under two distinct categories: continuous models [1–3] and discrete models [4,5]. Both represent a coarse grained description of a very complicated physicochemical system and the use of one or the other depends on the quantities one is interested in. For example, continuous models are very useful to investigate the role of an external force on chemical kinetics [6], since the external force is inserted into the Fokker-Planck (FP) equations without any ambiguity. This is no longer true for discrete models, when one has to resort to some *ad hoc* principle or *a priori* reasoning to insert force in transition rates [4]. Nonetheless, discrete models present the important advantage of being analytically solvable, as it happens, for instance, in jump processes [7]. On the other hand, an analytical solution is quite difficult to obtain in the general case of continuous models, and one has to resort to complex numerical integrations. In this paper, we introduce a discrete model, similar to the ones proposed in [4] and [5], but with the following constraint: if a is the lattice distance between subsequent spatial positions of the system, the continuous model should be obtained as a limit of the discrete one for $a \to 0$. The connection between a kinetic theory involving activated transitions over potential-energy barriers and a diffusion theory approach based on a FP equation dates back to Kramers [8], (see [9], for a recent review). In [10], the idea was applied to models for protein motors, but the force dependence was left in equal apportionments over backward and forward transition rates and the experimental results on the force dependence of the apparent Michaelis constant [11] were not available. In [12], a general theory for motor proteins was presented. This theory was developed in a two-dimensional manifold and complex integrations over state variables were used to calculate force-dependent transition rates over potential barriers in a discrete model. In the present paper, we do not use complex integrations; instead, we identify in the generalized detailed balance the condition for a discrete model to be compatible with a continuous one. Few parameters are needed to capture the overall shape of

the potential-energy surface that is no longer needed in full detail. Detailed balance was used in [13] to calculate transition rates for particles diffusing over potential barriers. The obtained discrete kinetics model led to a fast and reliable numerical procedure to calculate mean velocity of correlation ratchets. A model similar to ours was also developed in [14] in the context of thermal ratchets, even if no connection with the actual chemistry of motor proteins was done. Moreover, motor proteins are isothermal, and therefore, are better described by correlation ratchets. In [15], a master equation approach was used to investigate the force generation in RNA polymerase, which may be considered a motor protein, even if it differs from kinesin, myosin, and dynein, both in structure and function. In Sec. I, we outline the general framework, which may be useful not only for modeling molecular motors, but also any mechanochemical cyclic system. In the general formulation of our model, the chemical reaction coordinate is treated on an equal footing as the spatial one. Onsager reciprocity relations will be shown to hold in the most general case in the stationary periodic close to equilibrium state, provided detailed balance is verified. In Sec. II, we specify our model to the context of molecular motors. We show that our model may be regarded as the discrete analogue of the continuous one proposed in [2,3], leading to a clear interpretation of the generalized forces and currents introduced in Sec. I. In Sec. III, a discrete chemical kinetics model with a generalized detailed balance condition is defined for the case of motor proteins. Semiphenomenological considerations help to decide the apportionments of generalized forces over forward and backward transitions. In Sec. IV, two example models are studied and their predictions compared with experimental data.

I. GENERAL FRAMEWORK

Our model will describe the time evolution of a thermodynamic out-of-equilibrium system in a complex phase space. The state of the system (a motor protein, an ion pump, or whatsoever) is determined by the thermodynamic parameters x_α ($\alpha = 1 \ldots, d$). One of these parameters may represent the position of the protein center of mass, another a

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chemical reaction coordinate (or a variable indicating the conformation of the protein), and so on. In general, the number of these thermodynamic parameters (and hence, the dimensionality of the system under study) is sufficient to identify the state of the system by a direct experimental measure. Therefore, we will assume the state of the system to be described by a d-dimensional vector X subject to a time evolution in a d-dimensional discrete phase space, which may be mapped on $\mathcal{Z}^d$ (in general, the lattice spacing in each direction will be different).

The probability of being in a particular state X at time t is written as $P_X(t)$. Since the system must be in one of the X states, the normalization condition follows

$$\sum_X P_X(t) = 1 \forall t. \tag{1}$$

W_{XY} is defined as the transition probability per unit time from state Y to state X and it is assumed to be time independent.

Another hypothesis is the full periodicity along any direction α. This is usually assumed for all models of motor proteins, (see [10,12]). The periodicity N_α depends on α, but we assume $N_\alpha \geq 1$, since it is always possible to reduce the steps until this constraint is satisfied. In other words, we assume that the state described by the parameters $(l_1 N_1 + x_1, \ldots, l_d N_d + x_d)$ with $L \equiv \{l_1, \ldots l_d\} \in \mathcal{Z}^d$ is equivalent to the state described by the parameters $(x_1, \ldots, x_d)$.

We introduce the variable

$$\chi_X = \begin{cases} 1 & \text{for } 1 \leq x_\alpha < N_\alpha \quad \forall \alpha \in \{1, \ldots, d\} \\ 0 & \text{otherwise} \end{cases}, \tag{2}$$

which is an indicator of the period in which the system is moving and will be useful for subsequent calculations.

The time evolution of the system is simply given by the master equation

$$\dot{P}_X = \sum_Y (W_{XY} P_Y - W_{YX} P_X) \equiv \sum_Y L_{XY} P_Y, \tag{3}$$

where we have defined

$$L_{XY} = W_{XY} - \delta_{XY} \sum_Z W_{ZX}. \tag{4}$$

From this definition, it follows

$$\sum_X L_{XY} = 0 \Rightarrow \sum_X \dot{P}_X = 0, \tag{5}$$

which is consistent with the normalization condition, Eq. (1). Since the system is assumed to be periodic,

$$W_{X+LN, Y+LN} = W_{XY} \quad \forall L \in \mathcal{Z}^d, \tag{6}$$

where $LN \equiv (l_1 N_1, \ldots, l_d N_d)$. It is simple to show that the same rule holds also for the matrix L_{XY}, defined in Eq. (4).

We introduce a time-independent variable q_X, depending explicitly on the X coordinate, i.e., on the state of the system. We define the current J_q conjugated to the variable q_X

$$J_q = \frac{d\langle q \rangle}{dt}, \tag{7}$$

where $\langle q \rangle$ is the average $\langle q \rangle = \Sigma_X q_X P_X$. By applying Eqs. (3) and (5) it easily follows that

$$J_q = \sum_{XY} (q_X - q_Y) L_{XY} P_Y. \tag{8}$$

We introduce probabilities and transition rates over all periods, following some of the formalism of the $d=1$ case studied in [7]

$$R_X \equiv \sum_L P_{X+LN}, \tag{9}$$

$$\mathcal{L}_{XY} \equiv \sum_L L_{X,Y+LN}. \tag{10}$$

By definition, R_X is a periodic quantity. It is easy to show that also $\mathcal{L}_{XY}$ is periodic in both arguments X and Y. At variance of L_{XY}, $\mathcal{L}_{XY}$ is a finite matrix; also R_X is a finite vector, whereas P_X is not. From the time evolution of P_X, we may easily obtain the time evolution of R_X

$$\dot{R}_X = \sum_Y L_{XY} R_Y. \tag{11}$$

For any variable f_Y and using Eq. (2), the following property holds

$$\sum_X f_X = \sum_X \chi_X \sum_L f_{X+LN}. \tag{12}$$

Applying property (12) to Eq. (11) and the periodicity of R, we obtain

$$\dot{R}_X = \sum_Y{}' \mathcal{L}_{XY} R_Y, \tag{13}$$

where, by definition, $\Sigma_Y' = \Sigma_Y \chi_Y$, i.e., a primed sum is restricted only to one period along any axis. This is a master equation for a system with a finite number ($\Pi_{\alpha=1}^d N_\alpha$) of states. The $\mathcal{L}_{XY}$ matrix is finite and has the following properties:

$$\mathcal{L}_{XY} \geq 0 \quad \text{for } X \neq Y, \tag{14}$$

$$\sum_X{}' \mathcal{L}_{XY} = 0 \quad \forall Y \in \mathcal{Z}^d. \tag{15}$$

It is easy to show, by applying Eqs. (12) and (5), that

$$\sum_X{}' R_X = \sum_X P_X = 1. \tag{16}$$

Therefore, there exists a stationary solution $\hat{R}_X$ of Eq. (13) and, under general hypotheses (always satisfied in the examples treated in the next sections), it is unique [16]. It is also periodic, by definition.

If $q_X = x_\alpha$ for any value of α, then $q_X - q_Y = q_{X+LN} - q_{Y+LN}$ is also periodic, and we may rewrite the current as

$$J_q = \sum_{XY} \chi_Y(q_X - q_Y)L_{XY}R_Y, \quad q_X = x_\alpha. \quad (17)$$

A subsequent application of property (12) to Eq. (17) gives

$$J_q = \sum_{XY} \chi_X(q_X - q_Y)L_{XY}R_Y, \quad q_X = x_\alpha \quad (18)$$

and, after some manipulation, we obtain the following expression:

$$J_q = \sum_{XY} \frac{\chi_X + \chi_Y}{4}(q_X - q_Y)(L_{XY}R_Y - L_{YX}R_X), \quad (19)$$

where the argument in the sum is evidently symmetric under a change $X \leftrightarrow Y$.

If the detailed balance condition for the periodic stationary state, $R_X = \hat{R}_X$, holds

$$W_{XY}\hat{R}_Y = W_{YX}\hat{R}_X, \quad (20)$$

which is equivalent to the following:

$$L_{XY}\hat{R}_Y = L_{YX}\hat{R}_X, \quad (21)$$

then from Eq. (19), the net stationary current is zero.[1] A net flow, i.e., a nonzero stationary current, may occur only if the detailed balance condition Eq. (20) is violated. This can be done in several ways: in the continuous model proposed in Ref. [3], for instance, detailed balance holds separately for each chemical reaction, introducing the chemical potential $\Delta\mu$. In our model, we introduce a set of generalized forces, able to drive the system out of equilibrium, so that a finite stationary current may occur. Each generalized force f_α is coupled to one generalized coordinate x_α. Both the transition matrix L_{XY} and the stationary solution will depend explicitly on the force vector F, so that

$$\sum_Y{}' \mathcal{L}_{XY}(F)\hat{R}_Y(F) = 0. \quad (22)$$

Of course, at equilibrium, $F = 0$ and the stationary currents are all identically zero. Our assumption is that condition (20) is replaced by a generalized detailed balance condition (in this section and in the Appendix, the factor $\beta = 1/k_BT$ is absorbed in the definition of F)

$$L_{XY}(F)\hat{R}_Y(0)e^{F \cdot Y} = L_{YX}(F)\hat{R}_X(0)e^{F \cdot X}. \quad (23)$$

We remark that the stationary solution $\hat{R}_X(F)$ does not satisfy a detailed balance condition

$$L_{XY}(F)\hat{R}_Y(F) \neq L_{YX}(F)\hat{R}_X(F). \quad (24)$$

An equality in Eq. (24) would imply that $\hat{R}_Y(F)$ could be written as

$$\hat{R}_X(F) \propto \hat{R}_X(0)e^{F \cdot X}, \quad (25)$$

which is, evidently, not periodic.

In a local thermodynamic equilibrium, the generalized stationary currents may be written in the following form:

$$\hat{J}_{x_\alpha} = \sum_{\beta=1}^{d} \lambda_{\alpha\beta}f_\beta. \quad (26)$$

The coefficients $\lambda_{\alpha\beta}$ are called Onsager coefficients. In general, even when the linear approximation cannot be applied, we may define

$$\lambda_{\alpha\beta} = \frac{\partial \hat{J}_{x_\alpha}}{\partial f_\beta}. \quad (27)$$

We show in the Appendix that, provided the generalized detailed balance condition Eq. (23) holds, these coefficients verify the generalized Gyarmati-Li [17] reciprocal relations

$$\lambda_{\alpha\beta} = \lambda_{\beta\alpha} \quad \forall \alpha, \beta \in \{1, \dots, d\} \quad (28)$$

and, hence, the Onsager reciprocity relations. These properties are general and do not depend on the specific parameters of the model and are based on the generalized detailed balance condition Eq. (23). This condition is a common assumption also for continuous models, as discussed further in the next section.

II. CONTINUUM LIMIT FOR MOLECULAR MOTORS

The usual choice for molecular motors is a two-dimensional manifold in which one direction represents the position of the center of mass along the linear track (the microtubule or the actin filament). The other is the reaction coordinate for the ATP hydrolysis, (see [12]), which is also related to the conformational changes of the motor protein. These conformational changes are commonly thought to occur after binding ATP and release of reaction products adenosine diphosphate (ADP) and P_i [18].

The transition rates will be therefore written as W_{xy}^{nm} where the subscript xy denotes a transition from spatial position y to spatial position x whereas the superscript nm stands for a transition from a state with m ATP molecules to a state with n ones.[2] Of course, this variable may also repre-

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[1]Notice that if Eq. (21) holds, then also $\mathcal{L}_{XY}\hat{R}_Y = \mathcal{L}_{YX}\hat{R}_X$ holds, but the converse is not guaranteed to be true.

[2]Using the definitions of the previous section, the spatial and chemical directions correspond to $\alpha = 1$ and $\alpha = 2$, respectively.

sent a noninteger chemical reaction coordinate (accounting for multiple states models), but this is the simplest possible choice. The periodicity is not specified for the spatial direction, while it is one for the chemical direction, i.e., we are assuming that the state of the motor in presence of n ATP molecules is equivalent to the one in presence of $n+1$ ATP molecules. We remark that this assumption does not mean that a thermodynamic system with n ATP molecules is equivalent to the same thermodynamic system with $n+1$ ATP molecules, but only that the chemical state of the motor protein after the reaction cycle is completed (and 1 ATP molecule is consumed or produced) is equivalent to the state it was before entering the cycle. We allow only transitions from a position x to $x+a$ and $x-a$. All other transition rates will be identically zero. Chemical transitions, i.e., those involving the superscripts nm (with $n \neq m$) will be specified later. At the moment, we only use transition rates in the form[3] $w_{xy} = \Sigma_m W_{xy}^{nm}$. According to the definition Eq. (9) and due to our choice of periodicity one in the chemical reaction coordinate, the master equation for the rate of change of R_x, or Eq. (11) is

$$\dot{R}_x = w_{x,x+a}R_{x+a} - w_{x+a,x}R_x + w_{x,x-a}R_{x-a} - w_{x-a,x}R_x.$$
$$(29)$$

We define a discrete current j_x

$$j_x = (w_{x+a,x}R_x - w_{x,x+a}R_{x+a}).$$
$$(30)$$

Applying this definition to Eq. (29)

$$\dot{R}_x = -(j_x - j_{x-a}) \equiv -a(\nabla_d j)_x,$$
$$(31)$$

where $(\nabla_d j)_x$ is, by definition, the discrete gradient of j_x.

In the continuum (FP) description

$$\dot{P}(x,t) = -\nabla j(x,t),$$
$$(32)$$

$$j(x,t) = \frac{D}{T}[-T\nabla P(x,t) - P(x,t)\nabla V(x) + P(x,t)f],$$
$$(33)$$

where T is the temperature, D the diffusion constant, $V(x)$ a periodic potential, f the force, and $j(x,t)$ is the probability density current. The potential $V(x)$ has the same period as the transition rates w_{xy}.

For very small values of a we define

$$R_x \equiv aP(x,t).$$
$$(34)$$

If in Eq. (30) we expand R_{x+a} to the first order in a, the discrete current may be rewritten as

$$j_x = R_x(w_{x+a,x} - w_{x,x+a}) - a(\nabla R_x)w_{x,x+a}.$$
$$(35)$$

Using Eqs. (31), (32), and (34), for very small a, one gets

$$j_x = j(x,t).$$
$$(36)$$

By means of this correspondence, Eq. (36), and using Eqs. (33) and (35), we obtain

$$D = a^2 w_{x,x+a},$$
$$(37)$$

$$-D\nabla V(x) + Df = a(w_{x+a,x} - w_{x,x+a}).$$
$$(38)$$

Solving for $w_{x+a,x}$

$$w_{x+a,x} = w_{x,x+a}[1 - a\beta[\nabla V(x) - f]],$$
$$(39)$$

where Eq. (37) has been used. If we suppose that the following relation holds:

$$w_{x+a,x} = w_{x,x+a}e^{-\beta[V(x+a)-V(x)-af]},$$
$$(40)$$

then, Eq. (39) is satisfied in the continuum limit ($a \to 0$).

This relation corresponds to the standard detailed balance condition when $f = 0$ and the stationary periodic solution is

$$\hat{R}_x(0) \propto e^{-\beta V(x)},$$
$$(41)$$

whereas Eq. (40) corresponds to a generalized detailed balance condition Eq. (23), when $f \neq 0$.

A. The chemical reaction

By analogy with the continuum model [2], we suppose that each transition rate W_{xy}^{nm} is essentially due to three subprocesses, leading to ATP consumption (α transitions in [3]), ATP production (γ), and no change in ATP concentration or thermal transitions (β).

Since a chemical reaction is present in α and γ processes, the chemical potential difference $\Delta\mu = \mu_{ATP} - \mu_{ADP} - \mu_{Pi}$ plays the role of a generalized force, conjugated to the number of ATP molecules. In this paper, only transitions from $m = n + \Delta n$ to n ATP molecules with $\Delta n = \pm 1, 0$ will be considered.

The generalized detailed balance condition Eq. (23) is therefore

$$\frac{W_{x+a,x}^{n,n+\Delta n}}{W_{x,x+a}^{n+\Delta n,n}} = e^{-\beta[V(x+u)-V(x)-fa-\Delta n\Delta\mu]},$$
$$(42)$$

where $e^{-\beta V(x)} \propto \hat{R}_x(0)$ is the stationary equilibrium solution when all generalized forces are zero. Transitions with $\Delta n > 0(<0)$ correspond to ATP consumption (production). Equation (42) states that when $\Delta\mu > 0(\Delta\mu < 0)$ transitions leading to ATP consumption (production) are more favorable and lead to a spatial advancement of the motor. This is the core of the energy transduction process: chemical energy is used to perform mechanical work against a load $-f$ or chemical energy is produced performing a mechanical work on the protein. Notice that, according to our choice of notation, $f_1 = \beta f$ and $f_2 = -\beta\Delta\mu$.

These generalized detailed balance conditions are the same introduced in [3], in the limit $a \to 0$. We remark that this scheme corresponds to a periodicity one in the chemical reaction coordinate. A different periodicity in the chemical

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[3]The dependence on n is no more necessary, since W_{xy}^{nm} is periodic in n and m with period one.

coordinate would allow us to introduce different potential shapes $V(x,\xi)$ for each value of the reaction coordinate ξ, as for instance in [5]. Using periodicity two in the chemical coordinate, the continuous two-state model [2,3] is fully recovered in the $a \to 0$ limit with the same detailed balance conditions as in [2,3]. Indeed, using periodicity 2 for the chemical coordinate, if we allow only transitions between neighboring sites both in the spatial and chemical coordinate, Eq. (11) becomes

$$\dot{R}_x^1 = W_{x,x+a}^{11} R_{x+a}^1 - W_{x+a,x}^{11} R_x^1 + W_{x,x-a}^{11} R_{x-a}^1 - W_{x-a,x}^{11} R_x^1$$
$$+ W_{xx}^{12} R_x^2 - W_{xx}^{21} R_x^1, \tag{43}$$

$$\dot{R}_x^2 = W_{x,x+a}^{22} R_{x+a}^2 - W_{x+a,x}^{22} R_x^2 + W_{x,x-a}^{22} R_{x-a}^2 - W_{x-a,x}^{22} R_x^2$$
$$+ W_{xx}^{21} R_x^1 - W_{xx}^{12} R_x^2, \tag{44}$$

where 1 and 2 represent the two conformational state indexes and not the number of ATP molecules. In the continuum limit, this model is perfectly equivalent to the ones proposed in [2,3], with the following substitutions: $w_{x,x\pm a} = W_{x,x\pm a}^{ii}$, $V(x) = V_i(x)$, $i = 1, 2$ in Eq. (40) and $W_{xx}^{12} = \omega_2(x)$, $W_{xx}^{21} = \omega_1(x)$ in Eqs. (43)–(44) in the notation of Refs. [2,3]. The effective mobility ξ^{-1} of Refs. [2,3] is $\beta a^2 W_{x,x+a}^{ii}$. The general scheme introduced here allows us to treat the chemical and mechanical coordinates on an equal footing and write the detailed balance condition in a more standard and transparent way.

B. Generalized currents

According to the definitions given in Sec. I, the stationary current $\hat{J}_t$ (t stays for translational motion), associated to the protein center of mass corresponds to the velocity of the motor protein. Its full expression is given by

$$\hat{J}_t = a \sum_x{}' [w_{x+a,x} - w_{x-a,x}] \hat{R}_x, \tag{45}$$

whereas the stationary current $\hat{J}_c$ associated to the chemical coordinate is

$$\hat{J}_c = \sum_x{}' (W_{x+a,x}^{n,n+1} + W_{x-a,x}^{n,n+1} - W_{x+a,x}^{n,n-1} - W_{x-a,x}^{n,n-1}) \hat{R}_x, \tag{46}$$

which does not depend on n since $W_{xy}^{nm} = W_{xy}^{n+1,m+1}$. This current corresponds to the number of ATP molecules consumed per unit time, so we will refer to it as the "rate of ATP consumption." Notice that this current has the opposite sign of the one in Eq. (19). This is consistent with the above choice $f_2 = -\beta \Delta \mu$. We remark that β transitions do not contribute to ATP production since they do not involve any chemical reaction. These considerations will be used in the next section to develop and fully characterize a very simple discrete model whose continuum limit is still described by a Fokker-Planck equation.

III. DEFINITION OF THE MODEL

We showed that Eq. (40), i.e., a generalized detailed balance condition, is sufficient for a discrete model to be compatible with a Fokker-Planck equation in the continuum limit. Actually, Eq. (40) is compatible with a very general class of models, for which any apportionment of force f and chemical potential difference $\Delta \mu$ over forward (in space) and backward transitions, is perfectly reasonable. This is true as long as each transition allows the protein to take a substep that may be made infinitesimally small. If this is not possible for some of these substeps, the simple Fokker-Planck equation may not be able to describe the system in the continuum limit. Nevertheless, the Onsager relations still hold, as long as Eq. (23) holds and provided that the sum of all substeps is equal to one period. The continuum limit, left alone, is therefore not sufficient to fix the parameters required to define discrete models.

To be as general as possible, we use forward (u_j) and backward (w_j) transition rates, with *a priori* not specified apportionments

$$u_j(f, \Delta \mu) = \omega_j(f, \Delta \mu) e^{\beta(-v_j + a_j^+ f + m_j^+ \Delta \mu)}, \tag{47}$$

$$w_j(f, \Delta \mu) = \omega_j(f, \Delta \mu) e^{\beta(-a_j^- f - m_j^- \Delta \mu)}, \tag{48}$$

where v_j is the potential difference between states $j+1$ and j while $\omega_j(0,0)$ corresponds to a spontaneous transition probability from state j to state $j+1$ in the absence of any potential difference and generalized force. Since the potential is periodic, the v_j's are subject to the condition $\Sigma_j v_j = 0$. In the absence of any potential difference and generalized force, the particle may diffuse in both directions, so $u_j(0,0) = w_j(0,0) = \omega_j(0,0)$. This choice corresponds to a FP equation in two dimensions where both the spatial and chemical coordinates, as well as their associated generalized forces, are treated on an equal footing. This equation may be written in the following form:

$$\frac{\partial P(x,\xi,t)}{\partial t} = -\frac{\partial J_1(x,\xi,t)}{\partial x} - \frac{\partial J_2(x,\xi,t)}{\partial \xi}, \tag{49}$$

$$J_1 = D_1 \left[-T \frac{\partial P(x,\xi,t)}{\partial x} - P(x,\xi,t) \frac{\partial V(x,\xi)}{\partial x} + P(x,\xi,t)g \right], \tag{50}$$

$$J_2 = D_2 \left[-T \frac{\partial P(x,\xi,t)}{\partial \xi} - P(x,\xi,t) \frac{\partial V(x,\xi)}{\partial \xi} + P(x,\xi,t)\Delta \mu \right], \tag{51}$$

where x and ξ are, respectively, the spatial and chemical coordinates.

According to Eq. (23), all sums $a_j^+ + a_j^- (m_j^+ + m_j^-)$ should be interpreted as the effective size of the spatial (chemical) substep taken by the motor protein. Some recent experiments [19] seem to suggest the existence of these small substeps. A substep may be of different types: only

positional ($m_j^+ + m_j^- = 0$), only chemical ($a_j^+ + a_j^- = 0$), or mixed. The f and $\Delta\mu$ dependence in the transition rates, u_j's and w_j's, accounts also for more complicated schemes that cannot be ruled out, in principle.

The substep size is unknown and it is related to the conformational changes involved after binding ATP, but on a purely theoretical basis, space may be discretized so as to obtain the largest unit of substep such that all "natural" substeps are multiples of this elementary unit. After all N substeps, a full spatial and chemical period has been covered, so that

$$\frac{a_j^+ + a_j^-}{p} = m_j^+ + m_j^- = \frac{1}{N}, \qquad (52)$$

where p is the typical spatial step performed by the motor. We assume that the ω_j for this elementary unit of substep do not depend on f and $\Delta\mu$. This hypothesis is commonly as-

sumed in discrete models for substeps of any size [4,5,10], whereas in our model, it is assumed only for these elementary substeps. For a natural substep, a more complicated force dependence of transition rates is possible, at least in principle.

At the same time, since in the absence of any internal potential or external generalized force, the probability to proceed in one direction or the other is simply given by the probability to diffuse by $1/N$ of a full period in both coordinates, we assume that ω_j does not depend on j and omit the subscript in the transition rates ω_j.

It is possible to show that such a model, in general, is not compatible with very simple requests, i.e., that the velocity of the motor saturates for high ATP concentrations, and that the velocity obeys a Michaelis law, as follows from the data of [6,11]. Indeed, using Eq. (52), it is possible to show that the velocity is given in general by (see [7]).

$$J_t = \frac{p\omega(e^{\beta\Delta\mu} - 1)}{\displaystyle\sum_{n=1}^{N} e^{\beta[v_n + (1 - m_n^+)\Delta\mu]}\left[1 + \sum_{i=1}^{N-1} e^{-\beta(i/N - 1/N + m_{n+i}^+ + m_n^-)\Delta\mu}\prod_{j=1}^{i} e^{\beta v_{n+j}}\right]}, \qquad (53)$$

in the case where $f = 0$. If all $m_n^\pm \geq 0$, in the large $\Delta\mu$ limit, the velocity is given by

$$J_t \approx \frac{p\omega}{\displaystyle\sum_n e^{\beta(v_n - m_n^+\Delta\mu)}}, \qquad (54)$$

which is exponentially large in $\Delta\mu$ unless all $m_n^+ = 0$. But this condition, together with the condition that $m_n^+ + m_n^- = 1/N$ implies that the velocity may be written in the form

$$J_t = \frac{A(q-1)}{K_N q + K_{N-1}q^{1-1/N} + \cdots + K_1 q^{1/N}}, \quad q = e^{\beta\Delta\mu}, \qquad (55)$$

where the constants K's do not depend on q and are model dependent. Equation (55) is not a Michaelis law, i.e., of the form $J_t = (Aq/K_M + q) - B$, even in the large q limit. This is true for any value of N except $N = 1$. Therefore, one such discrete model is compatible with a Michaelis law only if we concentrate all the chemical reaction in a single substep. Thus, let us assume now that the chemical reaction occurs in a single step, and without loss of generality, we suppose that this ATP-driven step is the first one in the cycle. We notice that this, in turn, would imply that the smallest substep is the one that occurs during ATP hydrolysis, which is reasonable.[4]

A graphical representation of this class of discrete models with only one chemical transition is given in Fig. 1, for the case where $N = 3$. Let $\Delta\mu$ be apportioned over the forward and backward transitions, so that $m_1^+ = \epsilon, m_1^- = 1 - \epsilon$. With some calculations, it is possible to show that in this case we obtain for velocity an expression of the type

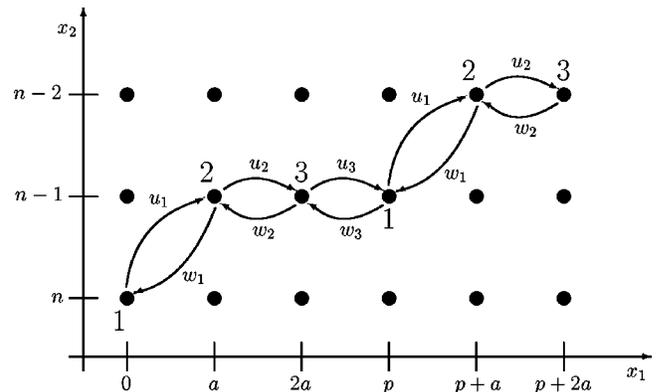$$J_t = \frac{A(q-1)}{Kq + K_1 q^\epsilon + K_2 q^{1-\epsilon}}, \qquad (56)$$

FIG. 1. Graphical representation of a discrete model, with $N = 3$ states along the spatial direction x_1. The chemical direction x_2 represents the number of ATP molecules. Conformational states of the motor protein are represented by the numbers 1, 2, 3. The system is periodic both in the spatial direction x_1 (periodicity p; $a = p/N = p/3$) and in the chemical direction (periodicity 1). Only transition rates u_1 and w_1 involve a chemical reaction, all the others are purely positional.

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[4]A net advancement of the protein center of mass is commonly thought to occur upon release of the reaction products, whereas the hydrolysis reaction does not seem to imply any net macroscopic rearrangement on its own [20].

which is still incompatible with a Michaelis law unless $\epsilon = 0$ or $\epsilon = 1$. Choosing one or the other leads essentially to the same Michaelis law, except some multiplicative parameters that, in turn, depend on the products $\omega e^{\beta v_j}$, and ought to be determined by experiments.

In the same way, the force apportionment may be investigated. The problem is that at variance of chemical potential, experimental data are obtained only for small forces. Therefore, it is not possible to use the same criteria since, to our knowledge, for high values of force, the velocity may grow up even to $\pm\infty$, meaning that the motor detaches from the fiber. Nevertheless, by the same line of reasoning, if we assume that the velocity should reach a constant value for high values of force in the positive direction, we find the condition

$$a_j^+ = 0 \quad \forall j = 1, \ldots, N. \tag{57}$$

On the contrary, if we assume that a constant velocity is reached only when the external force opposes the natural direction of movement (which is what one expects on the basis of the available data [11]), then we find the condition that

$$a_j^- = 0 \quad \forall j = 1, \ldots, N. \tag{58}$$

All intermediate cases, the symmetric one included, lead, therefore, to velocities growing up to $\pm\infty$ as the force tends to $\pm\infty$. Remarkably, this is what happens when using a FP equation with very high forces, since the probability distribution is not sensitive to the potential shape and becomes flat, i.e., velocity is a linear function of force. Of course, in a FP description, every apportionment is totally equivalent to any other, as long as we consider the small a limit. This is not true in the limit for very high forces, for which our deri-

vation of the continuum limit is no longer a good approximation. Therefore, it is not surprising that in discrete models, a particular choice of apportionment has dramatic consequences on the asymptotic behaviors of the quantities of interest, in the same way a different apportionment of the chemical potential leads to asymptotic behaviors that are not compatible with the expected Michaelis law unless, as shown above, the chemical reaction is concentrated in a single step. In the following section, we will study in detail some examples of models with spatial periodicity two and three highlighting their main predictions.

IV. MODEL PREDICTIONS AND EXAMPLE STUDIES

In all the following, lengths are measured in units of filament periods p, while potential difference, v_j, and chemical potentials, $\Delta\mu$, are measured in units of kT, forces, f, in units of kT/p. According to our previous discussion, since experimental data suggest that the velocity should reach a constant value for high-negative forces, we assume the force apportionment to be asymmetric and concentrated in the forward transitions. In the same way, we assume the first step to be chemically driven, so as to obtain a Michaelis law. We will show that these two hypotheses, left alone, are sufficient to obtain a force dependent Michaelis constant for velocity and rate of ATP consumption, and also some interesting predictions about effective step-size and randomness factor.

In these models

$$u_n = \omega e^{-v_n + f/N + \Delta\mu\delta_{n1}}, \tag{59}$$

$$w_n = \omega, \tag{60}$$

with the condition $\Sigma_n v_n = 0$. The expression for velocity, using Eqs. (59) and (60), is

$$J_t = \frac{p\omega(e^{\beta(\Delta\mu + f)} - 1)}{\sum\limits_{n=1}^{N} e^{v_n + (1 - \delta_{n1})\Delta\mu + (1 - 1/N)f}\left[1 + \sum\limits_{i=1}^{N-1} e^{-(i/N)f}\prod\limits_{j=1}^{i} e^{v_{n+j} - \delta_{n+j,1}\Delta\mu}\right]}. \tag{61}$$

Interestingly, the correct law for velocity is of the type

$$J_t = \frac{Aq}{K_M + q} - B, \tag{62}$$

where K_M is the Michaelis constant. The same result has also been obtained in [6] in the context of continuous models. Equation (61) may be used to calculate the "stall" force, i.e., the force for which the velocity is zero. This is simply given by

$$f_{\text{stall}} = -\Delta\mu. \tag{63}$$

The picture is, of course, very simplified. The experimental data reposted in [11] show that the stall load $(-f)$ increases with increasing ATP concentrations, but probably the dependence on $\Delta\mu$ is not as simple as in Eq. (63). However,

data in this parameter region are subject to large experimental errors, due to rapid detachment of beads from the microtubule under stall conditions, so a comparison with experiment, at present, may be only of qualitative nature.

The rate of ATP consumption follows from Eq. (46) and may be written as

$$J_c = \frac{u_1 R_1 - w_1 R_2}{\sum\limits_{n} R_n}. \tag{64}$$

Using Eqs. (61) and (64), it is possible to show that the rate of ATP consumption and the velocity, when measured in ATP molecules hydrolyzed per second and periods per second, respectively, are exactly the same quantity, so that the effective step size (the number of periods taken per hydrolyzed ATP molecule) is one, which is consistent with experi-

ments on kinesin [21]. This is no longer true if we use a more complicated scheme with pure thermal processes in addition to the normal ATP consuming ones, leading to transitions between different states: in this case, the effective step size may be smaller than one.

Using Eq. (61), it is possible to obtain an explicit expression for the force-dependent Michaelis constant; for simplicity, we concentrate on models with spatial periodicity two (two-state models) and three (three-state models). For two-state models $v_1 = v$, $v_2 = -v$, whereas for three-state models, we assume $v_1 = v$, $v_2 = -v/2$, $v_3 = -v/2$. This means that the chemical potential difference is used in the first transition to overcome the internal potential barrier v, while the other transitions are favored by the internal potential shape. The Michaelis constant of Eq. (62) is given by

$$K_M(2) = e^{2v} + 2e^{-f/2+v}, \qquad (65)$$

$$K_M(3) = \frac{2e^{3/2v} + 3e^{-f/3+v} + e^{f/3+2v}}{1 + 2e^{f/3+v/2}}, \qquad (66)$$

for two-state and three-state models, respectively. In both examples, the Michaelis constant grows exponentially with $-f$ (see discussion of Sec. III), in accordance with the recent experimental observation of an increase in the Michaelis constant with an applied load [11]. Interestingly, both models predict a constant value for K_M at high positive values of the force. We remark that experimental data on the Michaelis constant for positive forces, to our knowledge, are still unavailable.

Recently developed experimental techniques allowed us to measure the randomness parameter [22], defined as the long-time limit of the ratio between the variance of the protein position on the filament, $\langle x^2(t) \rangle - \langle x(t) \rangle^2$, and the product of its average position, $\langle x(t) \rangle$ and periodicity p

$$r = \lim_{t \to \infty} \frac{\langle x^2(t) \rangle - \langle x(t) \rangle^2}{\langle x(t) \rangle p}. \qquad (67)$$

In fact, the time resolution of experiments corresponds to the same order of magnitude of one hydrolysis event (typically milliseconds), while, at present, conformational changes leading to ATP hydrolysis cannot be directly measured. Nonetheless, they affect the statistical distribution of the protein movement and the randomness parameter.[5] The macroscopic diffusion coefficient D is defined so that: $\langle x^2(t) \rangle - \langle x(t) \rangle^2 = 2Dt$, while $\langle x(t) \rangle = Vt$, where V is the velocity. Therefore,

$$r = \frac{2D}{pV}. \qquad (68)$$

The expression for D is rather complicated, but still calculable for jump processes [7]. The randomness parameter

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[5]See [15] for a very interesting discussion on the relevance of the randomness parameter and the effective diffusion constant for mechanochemical transducers.
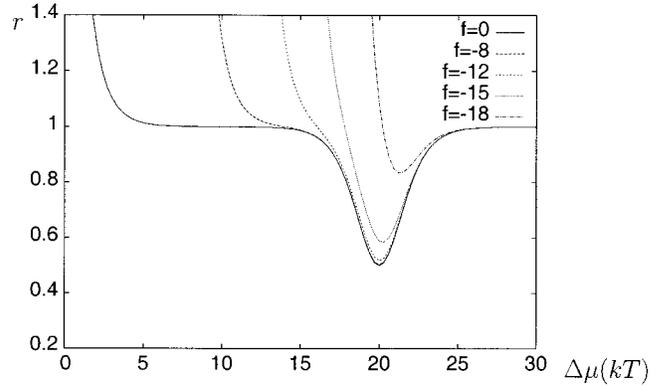

FIG. 2. Randomness parameter in a two-state model versus $\Delta\mu$, with $v = 10$ kT. Randomness approaches the value 1/2 when $\Delta\mu \approx 2v$, indicating that both transitions are rate limiting. At high $\Delta\mu$, there is only one rate-limiting transition, so that randomness approaches one. The force f is measured in units of kT/p.

presents some interesting properties [11,22,23]: first, $r = 0$ for a perfectly clocklike motor, whereas $r = 1$ for a "Poisson" motor with one biochemical transition and exponentially distributed time intervals between events. In general, r^{-1} provides a continuous measure of the number of rate-limiting transitions in the overall mechanochemical cycle (see [23] for a simple proof in the case of a jump process with equal forward and backward transition rates). In our models, the expressions for the randomness parameter may be easily calculated, but their expressions are rather cumbersome. Some important features can be directly inferred and compared with experiments.

At small loads $-f$ and small $\Delta\mu$, the velocity decreases linearly with both $-f$ and $\Delta\mu$, so that the randomness factor from Eq. (68) should approach ∞, assuming that the macroscopic diffusion coefficient approaches a constant value, in general, different from zero. This should be also verified under stall conditions, when the randomness factor again approaches ∞. At low values of $\Delta\mu$, but still sufficient to force the protein out of the stall condition, the randomness factor exhibits different behaviors, depending on force, as shown in Figs. 2 and 3. When $\Delta\mu < v$, the rate-limiting step is essentially the first one for both models, so the randomness factor approaches one when the stall condition is overcome. At intermediate values, $v < \Delta\mu < 2v$ for two-state models and $v < \Delta\mu < 3/2v$ for three-state models, the rate-limiting transition is still the first one, but its rate-limiting power is decreasing with respect to the others, due to the increase in $\Delta\mu$, so that the randomness parameter is decreasing, until at the border of this parameter region, $\Delta\mu \simeq v$ for two-state and $\Delta\mu \simeq (3/2)v$ for three-state models, all forward transition rates have essentially the same value: all steps are equally rate limiting, so that there are two rate-limiting steps for two-state models and three for three-state models. This is evident also in the figures; in this part of the graphs, the randomness parameter approaches 1/2 and 1/3 for two-state and three-state models, respectively. At very high ATP concentrations, the first step has a high-occurrence probability, whereas the other steps are rate limiting. This implies that the randomness parameter should approach a constant value
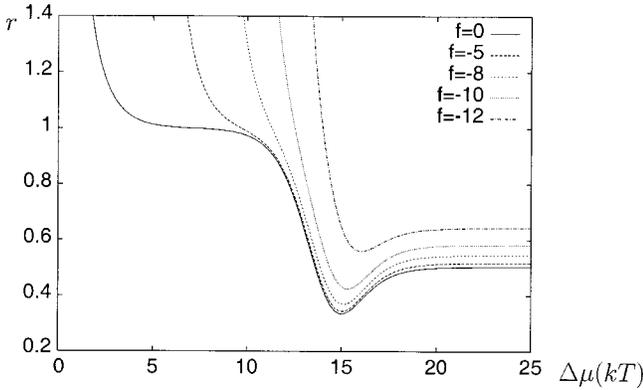
FIG. 3. Randomness parameter in a three-state model versus $\Delta\mu$, with $v = 10$ kT. Randomness approaches the value 1/3 when $\Delta\mu \approx 3v/2$, indicating that all transition rates are rate limiting. At high $\Delta\mu$, there are essentially two rate-limiting transition rates, so that randomness approaches 1/2, at least at low loads. The force f is measured in units of kT/p.

one for two-state models and 1/2 for three-state models. All these behaviors may be observed in the figures, at least for small values of force. Under very high loads, the velocity of the motor protein is very low in a wide range of $\Delta\mu$ values. This implies that the randomness factor is very high, until $\Delta\mu$ is high enough to force the system out of the stall condition. A direct comparison with experiments would be desirable. The central part of our figures reproduces data obtained for randomness in [11]. Our predictions in this parameter region also agree with theoretical derivations for continuous two-state ratchet models on kinesin [23], but in the case of continuous models, it is very difficult to calculate the randomness parameter at very high ATP concentrations, due to numerical problems. This is no longer true for discrete models, for which all complications are algebraic, rather than numerical. The experimental measure of randomness under very small loads or for small positive values of force should also be useful to infer, on a quantitative basis, the spatial periodicity necessary to fully characterize the system. Data in [11] seem to suggest a three-state model, since the randomness factor approaches a minimum value close to 1/3, but measurements at smaller loads would be useful to confirm or reject this hypothesis.

V. CONCLUSIONS

In this paper, we have introduced a master equation approach to describe interesting properties of molecular motors. Our approach is similar in spirit to a Kramers-Moyal expansion of the FP equation [24], but it is specifically studied for the problem of motor proteins, where both the mechanical and chemical coordinates are important. In this framework, we have studied the general conditions needed to obtain a discrete chemical kinetics model from a continuous one, when all generalized coordinates are treated on an equal footing. In this limit, a FP equation is recovered, when the requirement of a generalized detailed balance condition Eq. (23) is fulfilled in the out of equilibrium regime. This condition has been shown to imply the validity of the Onsager

reciprocity relations for the periodic stationary solutions in the close to equilibrium regime. This property is not surprising, since both Onsager relations and detailed balance are supposed to descend from microscopic reversibility. Motor proteins operate far from equilibrium, and far from the linear regime, where reciprocity relations are expected to hold. Nevertheless, reciprocity relations constitute a minimal requirement in a model for mechanochemical transduction, as stated by Hill [25] and, more recently, in the context of continuous models [3]. Moreover, to our knowledge, a proof for the case of discrete models, has never been given.

The continuum limit has been shown to be insufficient to fix all parameters in a discrete chemical kinetics model for any cyclic out-of-equilibrium thermodynamic system. However, in the case of motor proteins, semiphenomenological considerations led us to the formulation of discrete models that are compatible with the stochastic continuous ones in the continuum limit, satisfy the Onsager reciprocity relations and allow an easy comparison with experimental data.

We believe this paper to be useful to study the general conditions that ought to be verified by a discrete kinetics model and, most importantly, to study the force dependence of transition rates in mechanochemical processes. This is of relevance not only for research on motor proteins, but also on other important biomolecules.

APPENDIX: ONSAGER COEFFICIENTS AND RELATIONS

In this appendix, we will prove that, provided a generalized detailed balance condition in the form (23) holds, the Onsager relations Eq. (28) hold for any discrete model. We also provide a derivation of the Onsager coefficients and give their values for the case of two- and three-state models[6] studied in Sec. IV. In the following, we use the notation ∂_α to denote a partial derivative with respect to a generalized force f_α.

Differentiating both sides of Eq. (23), we obtain the condition

$$[[\partial_\alpha L_{XY}(F)]\hat{R}_Y(0) - [\partial_\alpha L_{YX}(F)]\hat{R}_X(0)]_{F=0}$$
$$= L_{XY}(0)\hat{R}_Y(0)(x_\alpha - y_\alpha). \tag{A1}$$

Differentiating the stationarity condition, Eq. (22), and applying Eq. (A1) we obtain, after some manipulation

$$\left[\sum_Y L_{XY}(F)\partial_\alpha R_Y(F)\right]_{F=0} = \sum_Y L_{XY}(0)\hat{R}_Y(0)(y_\alpha - x_\alpha). \tag{A2}$$

If $A_{XY} = A_{X+LN,Y+LN} \forall L \in \mathcal{Z}^d$

$$\sum_{XY} \chi_X A_{XY} = \sum_{XY} \chi_Y A_{XY} = \sum_{XY} \frac{\chi_X + \chi_Y}{2} A_{XY}, \tag{A3}$$

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[6] In these simplified models $J_c = J_t$, but this does not imply that the Onsager reciprocity relations are trivially satisfied. If they are, $J_c = J_t$ simply implies that all coefficients should be equal.

as a consequence of Eq. (12).

Replacing q_X with x_α in Eq. (19) and differentiating with respect to f_β, we obtain

$$\lambda_{\alpha\beta} = \sum_{XY} \frac{\chi_X + \chi_Y}{4} (x_\alpha - y_\alpha)[(\partial_\beta L_{XY})\hat{R}_Y - (\partial_\beta L_{YX})\hat{R}_X$$

$$+ L_{XY}(\partial_\beta \hat{R}_Y) - L_{YX}(\partial_\beta \hat{R}_X)]_{F=0}. \tag{A4}$$

Using condition (A1), we are left with

$$\lambda_{\alpha\beta} = \sum_{XY} \frac{\chi_X + \chi_Y}{4} (x_\alpha - y_\alpha)(x_\beta - y_\beta) L_{XY}(0)\hat{R}_Y(0)$$

$$+ \sum_{XY} \frac{\chi_X + \chi_Y}{4} (x_\alpha - y_\alpha)[L_{XY}(\partial_\beta \hat{R}_Y)$$

$$- L_{YX}(\partial_\beta \hat{R}_X)]_{F=0}. \tag{A5}$$

Applying the property (A3) to the quantities $(x_\alpha - y_\alpha)L_{XY}(0)(\partial_\beta \hat{R}_Y)$ and $(x_\alpha - y_\alpha)L_{YX}(0)(\partial_\beta \hat{R}_X)$ the Onsager coefficients are

$$\lambda_{\alpha\beta} = \sum_{XY} \frac{\chi_X + \chi_Y}{4} (x_\alpha - y_\alpha)(x_\beta - y_\beta) L_{XY}(0)\hat{R}_Y(0)$$

$$+ \frac{1}{2} \sum_{XY} (x_\alpha - y_\alpha)[\chi_Y L_{XY}(\partial_\beta \hat{R}_Y)$$

$$- \chi_X L_{YX}(\partial_\beta \hat{R}_X)]_{F=0}. \tag{A6}$$

A subsequent application of Eqs. (A2) and (23) leads to

$$\lambda_{\alpha\beta} = \sum_{XY} \frac{\chi_X + \chi_Y}{4} (x_\alpha - y_\alpha)(x_\beta - y_\beta) L_{XY}(0)\hat{R}_Y(0)$$

$$+ \frac{1}{2} \sum_{XY} \left[\chi_Y \frac{L_{YX}}{\hat{R}_Y} (\partial_\alpha \hat{R}_X)(\partial_\beta \hat{R}_Y) + \chi_X \frac{L_{XY}}{\hat{R}_X} (\partial_\alpha \hat{R}_Y) \right.$$

$$\left. \times (\partial_\beta \hat{R}_X) \right]_{F=0}. \tag{A7}$$

From Eq. (23) and another application of Eq. (A3), we finally obtain

$$\lambda_{\alpha\beta} = \sum_{XY} \frac{\chi_X + \chi_Y}{4} \left[(x_\alpha - y_\alpha)(x_\beta - y_\beta) L_{XY}(0)\hat{R}_Y(0) \right.$$

$$\left. + \frac{L_{XY}(0)}{\hat{R}_X(0)} A_{XY}(0) \right], \tag{A8}$$

with $A_{XY}(F) \equiv \partial_\alpha \hat{R}_X \partial_\beta \hat{R}_Y + \partial_\alpha \hat{R}_Y \partial_\beta \hat{R}_X$. Equation (A8) is evidently symmetric under a change $\alpha \leftrightarrow \beta$, so that finally the Onsager relations, Eq. (28), are verified. The quantities $A_{XY}(0)$ may be obtained by solving Eq. (13) at stationarity for a finite number of states.

1. Two-state models

For the two-state models defined in Sec. IV, the coefficient λ_{12} may be easily calculated; it is obtained from Eq. (A8), by making explicit the two contributions

$$\lambda_{12}^{(1)} = \sum_{XY} \frac{\chi_X + \chi_Y}{4} (x_t - y_t)(x_c - y_c) L_{XY}(0)\hat{R}_Y(0),$$

$$\tag{A9}$$

$$\lambda_{12}^{(2)} = \sum_{XY} \frac{\chi_X + \chi_Y}{4} \frac{L_{XY}(0)}{\hat{R}_X(0)} A_{XY}(0), \tag{A10}$$

where the subscript $t(c)$ means translational (chemical). After some manipulations, and bearing in mind that $x_t - y_t$ represents the spatial displacement from state Y to state X, while $x_c - y_c$ is the ATP consumption from state Y to state X (positive when ATP is consumed), we obtain

$$\lambda_{12}^{(1)} = \frac{w_1}{2} \frac{u_1 + w_2}{u_1 + u_2 + w_1 + w_2}, \tag{A11}$$

$$\lambda_{12}^{(2)} = \frac{u_1(u_2 w_2 - u_1 w_1)}{2(u_1 + w_2)(u_1 + u_2 + w_1 + w_2)}, \tag{A12}$$

where all u_i and v_i are calculated at $(f, \Delta\mu) = (0,0)$ and finally

$$\lambda_{12} = \frac{w_2^2 w_1 + 2u_1 w_1 w_2 + u_1 u_2 w_2}{2(u_1 + w_2)(u_1 + u_2 + w_1 + w_2)}. \tag{A13}$$

Using Eqs. (59) and (60), we find

$$\lambda_{12} = \frac{\omega}{e^{-v} + e^v + 2}. \tag{A14}$$

The same Onsager coefficient may be obtained by linearizing the expression for velocity, Eq. (61).

2. Three-state models

The calculation for the Onsager coefficient in three-models by a direct application of Eq. (A8) is rather long. Its value may be obtained by a direct linearization of Eq. (61):

$$\lambda_{12} = \frac{\omega}{e^{-v} + 2e^{-v/2} + 2e^{v/2} + e^v + 3}. \tag{A15}$$

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