Universal Aspects of the Chemomechanical Coupling for Molecular Motors

Reinhard Lipowsky

MPI für Kolloid– and Grenzflächenforschung, Am Mühlenberg, D–14476 Golm, Germany

The directed movement of molecular motors is studied theoretically within a general class of nonuniform ratchet models in which the motor can attain M internal states and undergo transitions between these states at K spatial locations. The functional relationship between the motor velocity and the concentration of the fuel molecule is analyzed for arbitrary values of M and K. This relationship is found to exhibit universal features which depend on the number of unbalanced transitions per motor cycle arising from the enzymatic motor activity. This agrees with experimental results on dimeric kinesin and is predicted to apply to other cytoskeletal motors.

A lot of experimental and theoretical effort has been recently devoted to the processive movement of molecular motors along filaments. Experimentally, it is now possible to observe the movement of single motors and to determine their motor properties as a function of different control parameters. Such studies have been performed, e.g., for cytoskeletal motors such as dimeric kinesin [1–9], monomeric kinesin [10], myosin V [11], and dynein [12–14] which move along microtubuli or actin filaments.

For dimeric kinesin, the motor velocity has been measured as a function of two control parameters, the concentration Γ of the fuel molecule ATP and the applied force F. The motor velocity v was observed to increase monotonically with Γ and to saturate for large Γ. In addition, the data for zero or small F could be well fitted by $v(\Gamma) \simeq v_{\max}\Gamma/(\Gamma_* + \Gamma)$ [1,3,5]. More recently, it was found that such a fit is even possible over the whole force range, $0 \leq |F| \leq 5.6$ pN, provided one uses F-dependent parameters $v_{\max}$ and Γ_* which leads to [9]

$$v(\Gamma, F) \simeq v_{\max}(F)\frac{\Gamma}{\Gamma_*(F) + \Gamma}. \qquad (1)$$

The latter relation, which represents a specific functional dependence of the velocity on the *two* parameters Γ and F, describes the data for one particular cytoskeletal motor. *Should such a relation hold for other motors as well?* In order to address this question, I study a rather large class of ratchet models in which the motor can attain M internal states and undergo transitions between these states at K spatial locations. The dependence of the velocity on the two control parameters Γ and F is obtained for *arbitrary* values of M and K, and is found to be determined by the number Q of unbalanced transitions arising from the enzymatic motor activity.

Most cytoskeletal motors have one or two enzymatic domains which correspond to $Q = 1$, 2, or 4 as discussed below [15]. The relation as given by (1) is found to apply to all models with $Q = 1$. For $Q \geq 2$, somewhat more general relationships are obtained in which the velocity

$v(\Gamma, F)$ is given by the ratio of two Γ-polynomials with F-dependent coefficients. The degree of both polynomials is at most Q and is further reduced in the presence of additional constraints or symmetries.

Theoretically, the main challenge arising from the chemomechanical coupling of molecular motors consists in the simultaneous modeling of chemical kinetics and mechanical movement [16–26]. Here, I will use the framework of composite Markov processes [27]. One important aspect of real motors to be incorporated into this framework is the interdependence of the biochemical cycle and the conformational state as emphasized by the French group [20,24,26].

The (M, K) models studied below represent generalizations of those studied in [20,24,26], which were restricted to $(M, K) = (2, 2)$. In addition, the (M, K) models considered here have localized transition rates which are parametrized in terms of delta functions while the $(2, 2)$ models in [20,24,26] had transition rates localized in finite spatial intervals. The latter distinction appears to be rather technical but it is, in fact, crucial since the delta-function parametrization makes it possible to analyze these models for arbitrary values of M and K.

Within the (M, K) models, the directed movement of the motor is described by one spatial coordinate x. For linear motors, this coordinate describes the displacement of the center of mass of the motor parallel to the filament. For a given value of x, the motor molecule must be bound to the filament but can still be in a variety of internal states or levels. If the motor has only one enzymatic domain or head, this head can attain a discrete number of states corresponding to (i) no substrate, (ii) adsorbed ATP, (iii) adsorbed ADP/P, and (iv) adsorbed ADP. In each of these states, the motor may adopt a different conformation which will experience different interactions with the filament. If the motor has two heads, a and b, one has three groups of levels corresponding to (I) two bound heads, (II) bound head a, and (III) bound head b. In this case, the motor molecule can build up internal stresses arising, e.g., from the rebinding of the unbound head to the filament [28]. A similar approach should apply to rotary

motors where x would represent an appropriate angular coordinate [29].

The stochastic dynamics of the motor is described by the probability densities $P_m(x, t)$ to find the motor at time t and position x in level m with $1 \leq m \leq M$. For a given position x, each probability density P_m may change (i) because of lateral diffusion in level m described by lateral currents J_m or (ii) because of transitions between the different levels. Therefore, the probability densities P_m satisfy the continuity equations $\partial P_m(x, t) / \partial t + \partial J_m(x, t) / \partial x = I_m(x, t)$ with the transition current densities I_m.

The lateral currents J_m depend on the molecular interaction potentials $U_m(x)$ and on the applied force F [30] and have the usual form [27,31]

$$J_m \equiv -D_o[\partial V_m(x) / \partial x + \partial/\partial x]P_m, \qquad (2)$$

with $V_m(x) \equiv (U_m(x) - Fx)/T$ where T is the temperature in energy units and the parameter D_o represents the small-scale diffusion coefficient. The interaction potentials U_m contain contributions from internal stresses within the motor molecule. The transition current densities I_m are given by

$$I_m \equiv \sum_n{}' [-P_m \Omega_{mn}(x) + P_n \Omega_{nm}(x)], \qquad (3)$$

where the prime indicates $n \neq m$, and the transition rates $\Omega_{mn}(x)$ from state m to state n are parametrized by

$$\Omega_{mn}(x) \equiv \sum_k \omega_{mn}(x_k)\ell_\Omega \delta(x - x_k), \qquad (4)$$

which depend on the transition rate constants $\omega_{mn}(x_k)$ at the K positions $x = x_k$ with $0 \leq x_1 < x_2 < \cdots < x_k < \ell$. The parameters ℓ and ℓ_Ω represent the period of the underlying molecular potentials and a molecular "localization" length, respectively, and $\delta(x)$ is Dirac's delta function. Thus, the nonuniform ratchet models studied here may be characterized by a discrete network of vertices $[x_k, m]$ corresponding to the transition locations x_k and to the internal states or levels m as shown in Fig. 1.

If there is no enzymatic activity, the system obeys detailed balance and one has $\Omega_{mn}(x) = \exp[-V_n(x) + V_m(x)]\Omega_{nm}(x)$ which implies $\omega_{mn}(x_k) = \exp[-V_n(x_k) + V_m(x_k)]\omega_{nm}(x_k)$ in (4). For convenience, the transition rate constants $\omega_{mn}(x_k)$ will now be denoted by ω_r with $1 \leq r \leq N$, where $N \leq KM(M - 1)$ is the total number of such rates, and will be divided up according to

$$\omega_r = \omega_r^{db} + \Delta_r \qquad (5)$$

with the balanced parts ω_r^{db} and the unbalanced parts Δ_r arising from the enzymatic activity.

To proceed, let us consider stationary states with $\partial P_m / \partial t = 0$ and total lateral current $J_{\text{tot}} \equiv \sum_m J_m = \text{const}$, and employ periodic boundary conditions for the interval $0 \leq x < \ell$. The total position probability $P_{\text{tot}} \equiv \sum_m P_m$ is normalized in such a way that this
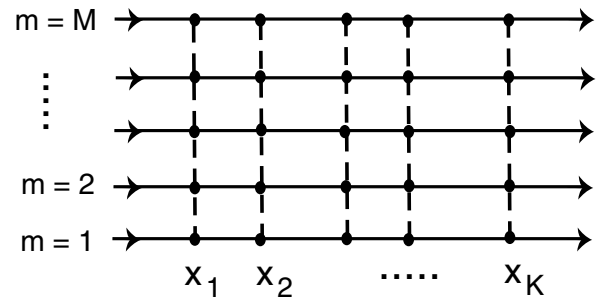

FIG. 1. Network of transitions at locations $x = x_k$ with $1 \leq k \leq K$ between different internal states or levels m with $1 \leq m \leq M$. Pairs of vertices $[x_i, m]$ and $[x_j, n]$ are connected by local lateral currents for $n = m$ and $i \neq j$ (corresponding to the full lines), and by local transition currents for $i = j$ and $n \neq m$ (corresponding to the broken lines). These currents obey a vertex rule which corresponds to Kirchhoff's first law for electric circuits. The arrows represent the periodic boundary conditions in the lateral direction.

interval contains one motor particle. This implies that the motor velocity v is given by $v = \ell J_{\text{tot}}$.

A detailed investigation of the (M, K) models just described shows that the dependence of the motor velocity v on the rate constants ω_r exhibits generic features which can be summarized by the following simple rules [32]:

Rule 0: The dependence of the motor velocity v on the transition rate constants ω_r has the form

$$v = \frac{\text{Pol}_1(\omega_1, \omega_2, \ldots, \omega_N)}{\text{Pol}_2(\omega_1, \omega_2, \ldots, \omega_N)}, \qquad (6)$$

with two polynomials Pol_1 and Pol_2.

Rule 1: Both polynomials are *multilinear* in all ω_r, i.e., each term of both Pol_1 and Pol_2 can be characterized by integers $z \equiv (z_1, \ldots, z_N)$ via

$$\text{term}(z) \sim \omega_1^{z_1} \omega_2^{z_2} \cdots \omega_N^{z_N} \qquad \text{with } z_r = 0, 1. \quad (7)$$

Rule 2: Each term contains at least $M - 1$ factors ω_r.

Rule 3: No term contains a product of the form $\omega_{mn}(x_k)\omega_{mo}(x_k)$.

Rule 4: No term contains a product of the form $\omega_{mn}(x_k)\omega_{nm}(x_k)$.

Rule 5: Pol_1 contains products of ω_r which correspond to closed and directed loops within the network of transitions. The smallest such loop involves a pair of transitions which connect two levels in opposite directions at different locations.

Rule 6: If all transition rates satisfy detailed balance with rate constants $\omega_r = \omega_r^{db}$, one has

$$v \sim \text{Pol}_1(\omega_1^{db}, \omega_2^{db}, \ldots) = 0 \qquad \text{for } F = 0. \quad (8)$$

Since the balanced transitions do not contribute to the motor velocity, let us now focus on the *unbalanced* transitions characterized by $\Delta_q > 0$ in (5). The total number of such transitions per motor cycle will be denoted by Q.

The simplest situation is provided by motors, such as monomeric kinesin, which have a single enzymatic domain. Such motors should have only one location x_k with

only one unbalanced transition rate which implies $Q = 1$. This situation is illustrated in Fig. 2(a) where the unbalanced transition with transition rate constant Δ_1 is indicated by a thick arrow. In this case, rule 1 leads to

$$v(\Delta_1) = \frac{a_0 + a_1\Delta_1}{b_0 + b_1\Delta_1} \qquad (9)$$

for $Q = 1$ where the coefficients a and b depend on F with $a_0(F = 0) = 0$ as follows from rule 6.

Next, consider molecular motors such as dimeric kinesin, dynein, or myosin V which have two identical enzymatic domains or heads. The corresponding ratchet models are characterized by two (usually different) locations with enzymatic activity. If each head can make (i) only forward steps or (ii) both forward and backward steps, it can be activated (i) at only one of these locations or (ii) at both locations, which corresponds to $Q = 2$ and $Q = 4$, respectively; see Figs. 2(b) and 2(c) [33].

For $Q = 2$, the dependence of the velocity on the unbalanced rate constants Δ_1 and Δ_2 has the general form

$$v(\Delta_1, \Delta_2) = \frac{a_0 + a_1\Delta_1 + a_2\Delta_2 + a_{12}\Delta_1\Delta_2}{b_0 + b_1\Delta_1 + b_2\Delta_2 + b_{12}\Delta_1\Delta_2}, \qquad (10)$$

with $a_0 = 0$ for $F = 0$. Likewise, for $Q \geq 3$, rule 1 implies that the motor velocity $v(\Delta_1, \ldots, \Delta_Q)$ is given by the ratio of two multilinear polynomials of degree Q, and rule 6 leads to $a_0 = 0$ for $F = 0$.

The generic features just described are valid for an arbitrary number of balanced transitions. Thus, we could add more and more balanced transitions in order to attain balanced rates $\Omega_{mn}^{db}(x)$ which vary continuously with x. This implies that the generic velocity-rate relationships should also be valid for transition rates

$$\Omega_{mn}(x) = \Omega_{mn}^{db}(x) + \sum_q \Delta_q \ell_\Omega \delta(x - x_q), \qquad (11)$$

where the functions $\Omega_{mn}^{db}(x)$ satisfy detailed balance but have an otherwise arbitrary x dependence and the summation over q depends on the level pair (m, n).

The velocity-rate relationships discussed so far represent the most general forms consistent with a given value of Q. If the motor cycle exhibits some additional constraints or symmetries, some of the F-dependent polynomial coefficients will be identically zero. One example is provided by $Q = 2$ with two unbalanced transitions which emanate from the same vertex $[x_k, m]$. In this case, one has $a_{12} = b_{12} = 0$ in (10) as follows from rule 3. Another example is provided by the *strongly unbalanced limit* in which one ignores all balanced transitions depicted as thin arrows in Figs. 2(a) and 2(b). In this limit, both relationships (9) and (10) simplify since rule 2 implies that the zeroth order coefficients a_0 and b_0 vanish for all F while the first order coefficients a_1 and a_2 now vanish for $F = 0$ as follows from rule 6.

In order to relate the theoretical results just described to experiments, one must include the dependence of the unbalanced rate constants Δ_q on the concentration Γ of the fuel molecules. The simplest scheme for an enzymatic reaction between the fuel molecules and the motor domain(s) is provided by Michaelis-Menten kinetics [34] which implies that $\Delta_q^{-1} = (c_q\Gamma)^{-1} + d_q^{-1}$ with $1 \leq q \leq Q$ where the reaction rates c_q and d_q may depend on the applied force F.

If these expressions for Δ_q are inserted into (9), one obtains the motor velocity

$$v(\Gamma, F) = \frac{g_0(F) + g_1(F)\Gamma}{h_0(F) + h_1(F)\Gamma} \qquad (12)$$

for $Q = 1$ with $g_0(F = 0) = 0$. Likewise, for $Q \geq 2$, the most general functional relationship is given by

$$v(\Gamma, F) = \left[\sum_{n=0}^{Q} g_n(F)\Gamma^n\right] \Bigg/ \left[\sum_{n=0}^{Q} h_n(F)\Gamma^n\right], \qquad (13)$$

with $g_0(F = 0) = 0$.

Models with $Q \geq 2$ can again lead to the simplest possible relationship (12) if some of the polynomial coefficients g_n and h_n vanish (for all F) because of additional constraints or symmetries. This happens, e.g., for models with $(M, K) = (2, 2)$ and $(M, K) = (3, 2)$ in the strongly unbalanced limit with $Q = 4$ which we have recently studied for dimeric kinesin [35]. The $(2, 2)$ models are characterized by the four transition rate constants $\omega_{12}(x_1) = \Delta_1$, $\omega_{21}(x_1) = \Delta_2$, $\omega_{12}(x_2) = \Delta_3$, and $\omega_{21}(x_2) = \Delta_4$. The symmetry between the two heads of dimeric kinesin implies $\Delta_4 = \Delta_1$ for forward steps and $\Delta_3 = \Delta_2$ for
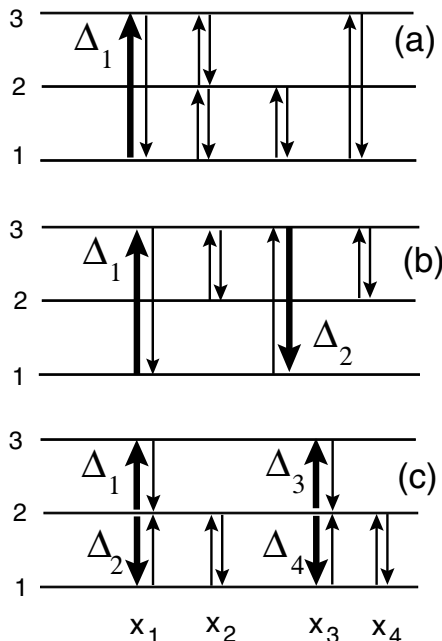

FIG. 2. Transition networks with $M = 3$ internal states or levels and with (a) $Q = 1$, (b) $Q = 2$, and (c) $Q = 4$ unbalanced transitions, respectively. In all three examples, the balanced and unbalanced transitions are indicated by thin and thick arrows, respectively. The unbalanced rate constants are denoted by Δ_q with $1 \leq q \leq Q$.

backward steps. If the corresponding Michaelis-Menten reaction rates c_q and d_q lead to a Γ-independent ratio Δ_2/Δ_1, one arrives again at the simplest form as given by (12) [35]. On the other hand, if the reaction rates do not have this property, the $(2,2)$ models with $Q = 4$ lead to Γ polynomials of degree 3, i.e., to a simplified version of (13) with $g_4 = h_4 \equiv 0$.

In summary, it has been shown here that the dependence of the motor velocity on the concentration Γ of the fuel molecules and on the applied force F is given by simple relationships which are primarily determined by the number Q of unbalanced transitions per motor cycle which break detailed balance. These relationships are *universal* in the sense that they are valid (i) for any choice of the molecular interaction potentials, (ii) for arbitrary applied force F, (iii) for any number of balanced transition rates, and (iv) for any force dependence of the Michaelis-Menten reaction rates. This universality has two important consequences. On the one hand, the functional relationships discussed here should apply to many types of real motors. On the other hand, it will in general be difficult to determine a unique set of model parameters for a specific molecular motor.

I thank Nicole Jaster for a critical reading of the manuscript.

---

[1] J. Howard, A. J. Hudspeth, and R. D. Vale, Nature (London) **342**, 154 (1989).

[2] K. Svoboda, C. Schmidt, B. Schnapp, and S. Block, Nature (London) **365**, 721 (1993).

[3] K. Svoboda and S. Block, Cell **77**, 773 (1994).

[4] M. J. Schnitzer and S. M. Block, Nature (London) **388**, 386 (1997).

[5] W. Hua, E. C. Young, M. L. Fleming, and J. Gelles, Nature (London) **388**, 390 (1997).

[6] W. O. Hancock and J. Howard, J. Cell Biol. **140**, 1395 (1998).

[7] M. Thormählen, A. Marx, S. A. Müller, Y.-H. Song, E.-M. Mandelkow, U. Aebi, and E. Mandelkow, J. Mol. Biol. **275**, 795 (1998).

[8] S. Gilbert, M. Moyer, and K. Johnson, Biochemistry **37**, 792 (1998).

[9] K. Visscher, M. J. Schnitzer, and S. M. Block, Nature (London) **400**, 184 (1999).

[10] Y. Okada and N. Hirokawa, Science **283**, 1152 (1999).

[11] A. D. Mehta, R. S. Rock, M. Rief, J. A. Spudich, M. S. Mooseker, and R. E. Cheney, Nature (London) **400**, 590 (1999).

[12] Z. Wang and M. P. Sheetz, Biophys. J. **78**, 1955 (2000).

[13] S. J. King and T. A. Schroer, Nature Cell Biol. **2**, 90 (2000).

[14] E. Hirakawa, H. Higuchi, and Y. Y. Toyoshima, Proc. Natl. Acad. Sci. U.S.A. **97**, 2533 (2000).

[15] For three-headed dyneins, the models studied here have up to $Q = 3 \times 3 = 9$ unbalanced transitions.

[16] A. F. Huxley, Prog. Biophys. Biophys. Chem. **7**, 257 (1957).

[17] S. Leibler and D. A. Huse, J. Cell Biol. **121**, 1357 (1993).

[18] M. O. Magnasco, Phys. Rev. Lett. **71**, 1477 (1993).

[19] R. Astumian and M. Bier, Phys. Rev. Lett. **72**, 1766 (1994).

[20] J. Prost, J.-F. Chauwin, L. Peliti, and A. Ajdari, Phys. Rev. Lett. **72**, 2652 (1994).

[21] C. Peskin and G. Oster, Biophys. J. **68**, 202s (1995).

[22] T. Harms and R. Lipowsky, Phys. Rev. Lett. **79**, 2895 (1997).

[23] L. Schimansky-Geier, M. Kschischo, and T. Fricke, Phys. Rev. Lett. **79**, 3335 (1997).

[24] F. Jülicher, A. Ajdari, and J. Prost, Rev. Mod. Phys. **69**, 1269 (1997).

[25] M. E. Fisher and A. Kolomeisky, Proc. Natl. Acad. Sci. U.S.A. **96**, 6597 (1999).

[26] A. Parmeggiani, F. Jülicher, A. Ajdari, and J. Prost, Phys. Rev. E **60**, 2127 (1999).

[27] N. van Kampen, *Stochastic Processes in Physics and Chemistry* (Elsevier, Amsterdam, 1992).

[28] The movement may also involve transverse displacements of the center of mass which could be incorporated via additional levels and, thus, via an increased value of M.

[29] An alternative scheme in which all degrees of freedom are continuous is discussed by D. Keller and C. Bustamente, Biophys. J. **78**, 541 (2000).

[30] The force F in (2) is the force component parallel to the filament. In optical trap experiments, the force often has a normal component which acts to detach the motor.

[31] H. Risken, *The Fokker-Planck Equation: Methods of Solution and Applications* (Springer Verlag, Berlin, 1989).

[32] The derivation of these rules is rather technical and will be described elsewhere.

[33] The two heads should act in a cooperative fashion; otherwise, the motor would frequently detach from the filament and, thus, would not be processive.

[34] See., e.g., A. L. Lehninger, D. L. Nelson, and M. M. Cox, *Principles of Biochemistry* (Worth Publishers, New York, 1993). In principle, the molecular motor could contain allosteric domains which bind regulatory molecules. The reaction rate Δ_q may then exhibit a sigmoidal dependence on Γ, which would lead to different v-Γ relationships.

[35] R. Lipowsky and T. Harms, Europ. Biophys. J. (to be published).