Kinesin's network of chemomechanical motor cycles – Appendices

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(Dated: April 26, 2007)

PACS numbers: 87.16.Nn, 87.16.Uv, 82.39.Fk
Keywords:

Appendix A. Parametrization of transition rates

The transition rates ω_{ij} are equal to the number of transitions $|ij\rangle$ from state i to state j per unit time. These transition rates depend on four control parameters: the load force F as well as on the molar concentrations of ATP, ADP, and P. In general, these rates have a finite value, $\omega_{ij,0}$, for vanishing force $F = 0$, and can thus be parametrized as

$$\omega_{ij} \equiv \omega_{ij,0}\, \Phi_{ij}(F) \quad \text{with} \quad \Phi_{ij}(0) \equiv 1 \tag{A.1}$$

which defines the force-dependent factors $\Phi_{ij}(F)$. Furthermore, all zero-force rates that describe the binding of one of the chemical species ATP, ADP, or P to one of the two motor heads depend on the corresponding molar concentrations $[X]$ with $[X] = [\mathrm{ATP}]$, $[\mathrm{ADP}]$, or $[\mathrm{P}]$. Thus, the zero-force rates of those transitions $|ij\rangle$ that involve binding of the chemical species X can be parametrized according to

$$\omega_{ij,0} \equiv \kappa_{ij}\, \mathcal{I}_{ij}([X]) \approx \kappa_{ij}\, [X] \tag{A.2}$$

with rate constants κ_{ij} where the second, asymptotic equality corresponds to dilute solutions. [1] For all transitions $|ij\rangle$ that do not involve the binding of ATP, ADP, or P, the factor $\mathcal{I}_{ij}([X])$ is simply given by $\mathcal{I}_{ij}([X]) \equiv 1$.

In the main text, the two relations (A.1) and (A.2) have been combined into the single equation

$$\omega_{ij} = \kappa_{ij}\, \mathcal{I}_{ij}([X])\, \Phi_{ij}(F)\,. \tag{1}$$

As an example, consider the 6-state model as introduced in Fig. 1(c) of the main text and supplemented in Fig. 4 by the binding and release of the chemical species ATP, ADP, and P. In this case, the transitions $|12\rangle$ and $|45\rangle$ describe binding of ATP which implies

$$\omega_{12,0} = \kappa_{12}\, \mathcal{I}_{12}([ATP]) \approx \kappa_{12}\, [ATP] \tag{A.3}$$

and

$$\omega_{45,0} = \kappa_{45}\, \mathcal{I}_{45}([ATP]) \approx \kappa_{45}\, [ATP] \tag{A.4}$$

where the asymptotic equalities again correspond to dilute solutions. Likewise, for the 6-state model in Fig. 1(c), ADP binding is described by the transitions $|65\rangle$ and $|32\rangle$ and P binding by $|16\rangle$ and $|43\rangle$ which implies the zero-force tansition rates

$$\omega_{65,0} = \kappa_{65}\, \mathcal{I}_{65}([ADP]) \approx \kappa_{65}\, [ADP], \tag{A.5}$$

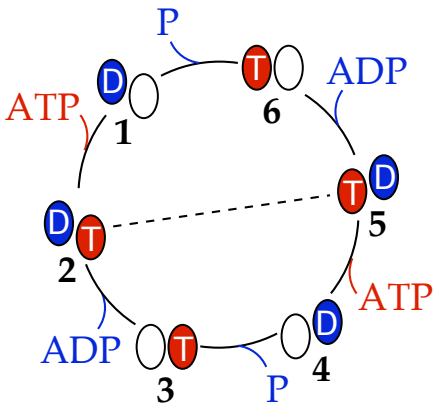

FIG. 4: Binding and release of the chemical species ATP, ADP, and P to and from the two motor heads within the 6-state model as introduced in Fig. 1(c) of the main text. As before, the broken line represents the mechanical forward step $|25\rangle$ and the mechanical backward step $|52\rangle$. During these mechanical transitions, the leading and the trailing head interchange their positions. For the forward cycle $\mathcal{F}^+$, ATP is bound to the leading head during the transition $|12\rangle$, ADP is released from the new leading head during $|56\rangle$, and P is released from the new trailing head during $|61\rangle$. For the reverse forward cycle $\mathcal{F}^-$, P is bound to the trailing head during the transition $|16\rangle$, ADP is bound to the leading head during $|65\rangle$, and ATP is released from the new leading head during $|21\rangle$. For the backward cycle $\mathcal{B}^+$, ATP is bound to the trailing head during the transition $|45\rangle$, ADP is released from the new trailing head during $|23\rangle$, and P is released from the new leading head during $|34\rangle$.

$$\omega_{32,0} = \kappa_{32}\, \mathcal{I}_{32}([ADP]) \approx \kappa_{32}\, [ADP], \tag{A.6}$$

$$\omega_{16,0} = \kappa_{16}\, \mathcal{I}_{16}([P]) \approx \kappa_{16}\, [P], \quad \text{and} \tag{A.7}$$

$$\omega_{43,0} = \kappa_{43}\, \mathcal{I}_{43}([P]) \approx \kappa_{43}\, [P]. \tag{A.8}$$

On the other hand, all transitions $|ij\rangle$ that describe ATP, ADP, or P release are independent of the molar concentrations and described by zero-force rates $\omega_{ij,0} = \kappa_{ij}$. The latter feature also applies to the mechanical transitions which are characterized by zero-force rates $\omega_{25,0} = \kappa_{25}$ and $\omega_{52,0} = \kappa_{52}$.

Appendix B. Steady state balance conditions

As discussed in the main text, each motor cycle $\mathcal{C}_\nu$ within a network model represents two directed cycles or dicycles, $\mathcal{C}_\nu^d$ with $d = \pm$, that differ in their orientation. As we previously showed in Ref. [2], each of these dicycles can be characterized by a steady state balance condition of the form

$$k_B T \sum{}' \ln\left(\frac{\omega_{ij}}{\omega_{ji}}\right) = E_{\rm ch}(\mathcal{C}_\nu^d) - W_{\rm me}(\mathcal{C}_\nu^d) \qquad (2)$$

where the prime at the summation sign indicates a summation over all di-edges $|ij\rangle$ of dicycle $\mathcal{C}_\nu^d$. In this way, one obtains a nontrivial relationship between the transition rates ω_{ij}, the chemical energy input $E_{\rm ch}$, and the mechanical work $W_{\rm me}$ for any dicycle of the network model.

In order to simplify the notation, it is convenient to rewrite the steady state balance condition (2) in terms of the transition energies [3]

$$E_{ij} \equiv k_B T \, \ln(\omega_{ij}/\omega_{ji}) = -E_{ij} \, . \qquad (B.1)$$

We then obtain the steady state balance condition in the form

$$\sum{}' E_{ij} = E_{\rm ch}(\mathcal{C}_\nu^d) - W_{\rm me}(\mathcal{C}_\nu^d) \qquad (B.2)$$

for each cycle $\mathcal{C}_\nu$ of the network. This condition characterizes the cycle $\mathcal{C}_\nu$ rather than the dicycle $\mathcal{C}_\nu^+$ since all terms in (B.2) merely change sign if we replace $\mathcal{C}_\nu^+$ by $\mathcal{C}_\nu^-$.

Each dicycle $\mathcal{C}_\nu^d$ may contain an integer number, $n_{\rm h}(\mathcal{C}_\nu^d) \geq 0$, of transitions that involve ATP hydrolysis as well as an integer number, $n_{\rm s}(\mathcal{C}_\nu^d) \geq 0$, of transitions that correspond to ATP synthesis. Because the network models contain all forward and backward transitions $|ij\rangle$ and $|ji\rangle$, these numbers satisfy $n_{\rm s}(\mathcal{C}_\nu^-) = n_{\rm h}(\mathcal{C}_\nu^+)$ and $n_{\rm h}(\mathcal{C}_\nu^-) = n_{\rm s}(\mathcal{C}_\nu^+)$ for all cycles $\mathcal{C}_\nu$. The chemical energy input per completed dicycle now depends on the molar concentrations [ATP], [ADP], and [P] and has the explicit form

$$E_{\rm ch}(\mathcal{C}_\nu^d) = [n_{\rm h}(\mathcal{C}_\nu^d) - n_{\rm s}(\mathcal{C}_\nu^d)]\Delta\mu \qquad (B.3)$$

with the energy change

$$\Delta\mu \equiv k_B T \, \ln(K_{eq}[ATP]/[ADP][P]) \, , \qquad (B.4)$$

per hydrolyzed ATP molecule where K_{eq} is the corresponding equilibrium constant. [4]

In addition, each dicycle leads to an integer number, $m_{\rm f}(\mathcal{C}_\nu^d) \geq 0$, of forward mechanical steps and to an integer number, $m_{\rm b}(\mathcal{C}_\nu^d) \geq 0$, of backward mechanical steps. Because all forward and backward transitions are included, one has $m_{\rm f}(\mathcal{C}_\nu^+) = m_{\rm b}(\mathcal{C}_\nu^-)$. For the 6-state and 7-state networks considered here, which contain only a single mechanical transition, the numbers $m_{\rm f}$ and $m_{\rm b}$ are either 0 or 1. In the presence of an external load force, F, the mechanical work performed by the motor during one completed dicycle is then given by

$$W_{\rm me}(\mathcal{C}_\nu^d) = [m_{\rm f}(\mathcal{C}_\nu^d) - m_{\rm b}(\mathcal{C}_\nu^d)] \, \ell \, F \, . \qquad (B.5)$$

where we have assumed that the step size of the motor is fixed. The latter assumption applies to kinesin.

As an example, let us consider the 6-state model in Fig. 1(c) and Fig. 4. The forward dicycle $\mathcal{F}^+ = |12561\rangle$ contains the ATP hydrolysis transition $|61\rangle$ and is, thus, characterized by $n_{\rm h}(\mathcal{F}^+) = 1$ and $n_{\rm s}(\mathcal{F}^+) = 0$. As the motor cycles through $\mathcal{F}^+$, the hydrolysis of a single ATP molecule is coupled to a forward mechanical step of size ℓ corresponding to the mechanical transition $|25\rangle$. The motor then performs the work $W_{\rm me}(\mathcal{F}^+) = +\ell F$ against the external force F. The steady state balance condition as given by (B.2) then has the form

$$E_{25} + E_{56} + E_{61} + E_{12} = \Delta\mu - \ell F \quad \text{for } \mathcal{F} \, . \qquad (B.6)$$

The backward dicycle $\mathcal{B}^+ = |45234\rangle$ contains the ATP hydrolysis transition $|34\rangle$ and is again characterized by $n_{\rm h}(\mathcal{B}^+) = 1$ and $n_{\rm s}(\mathcal{B}^+) = 0$. As the motor passes through the dicycle $\mathcal{B}^+$, the hydrolysis of a single ATP molecule is coupled to a backward mechanical step corresponding to the mechanical transition $|52\rangle$. The motor now performs the work $W_{\rm me}(\mathcal{B}^+) = -\ell F$. The resulting balance condition becomes

$$E_{52} + E_{23} + E_{34} + E_{45} = \Delta\mu + \ell F \quad \text{for } \mathcal{B} \, . \qquad (B.7)$$

Finally, the purely dissipative dicycle $\mathcal{D}^+ = |1234561\rangle$ is characterized by the hydrolysis of two ATP molecules during the transitions $|61\rangle$ and $|35\rangle$ and, thus, by $n_{\rm h}(\mathcal{D}^+) = 2$ and $n_{\rm s}(\mathcal{D}^+) = 0$. Since the motor does not undergo any mechanical transition and, thus, does not perform any work during this dicycle, we obtain the balance condition

$$E_{23} + E_{34} + E_{45} + E_{56} + E_{61} + E_{12} = 2\Delta\mu \text{ for } \mathcal{D} \, . \qquad (B.8)$$

The latter condition for $\mathcal{D}$ does not impose any additional constraint on the transition energies since it can be obtained by adding the two balance conditions (B.6) and (B.7) for the two cycles $\mathcal{F}$ and $\mathcal{B}$ and using the identity $E_{25} + E_{52} = 0$.

Appendix C. Force dependence of transition rates

If one inserts the parametrization of the transition rates ω_{ij} as given by (A.1) into the steady state balance condition (2), one can decompose this latter condition into a zero-part and a force-dependent part. For force $F = 0$, the mechanical work $W_{\rm me}$ vanishes, and the steady state balance condition (2) becomes

$$\begin{aligned} k_B T \sum{}' \ln\left(\tfrac{\omega_{ij,0}}{\omega_{ji,0}}\right) &= E_{\rm ch}(\mathcal{C}_\nu^d) \\ &= \left(n_{\rm h}(\mathcal{C}_\nu^d) - n_{\rm s}(\mathcal{C}_\nu^d)\right) \, \Delta\mu \, . \end{aligned} \qquad (C.1)$$

which relates the zero-force transition rates $\omega_{ij,0}$ to the free energy change $\Delta\mu$ per hydrolyzed ATP molecule. Substracting the zero-force balance condition as given by condition (C.1) from the full condition (2), we also obtain

$$k_B T \sum{}' \ln\left(\frac{\Phi_{ij}(F)}{\Phi_{ji}(F)}\right) = -W_{\rm me}(\mathcal{C}_\nu^d) = -\left[m_{\rm f}(\mathcal{C}_\nu^d) - m_{\rm b}(\mathcal{C}_\nu^d)\right]\ell\, F \tag{C.2}$$

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

Since no direct experimental information is available on the force dependence of the rate factors $\Phi_{ij}(F)$, they are parametrized in a particular simple way but required to fulfill the condition (C.2). For the mechanical transitions $|25\rangle$ and $|52\rangle$, we use the parametrization

$$\Phi_{25}(F) = e^{-\theta\bar{F}} \quad \text{and} \quad \Phi_{52}(F) = e^{(1-\theta)\bar{F}} \tag{C.3}$$

with the dimensionless force

$$\bar{F} \equiv \ell F/k_B T \tag{C.4}$$

and the dimensionless load distribution factor θ which satisfies $0 \le \theta \le 1$ as in [5]. For all chemical transition rates, we use

$$\Phi_{ij}(F) \equiv 2/(1 + e^{\,\chi_{ij}\bar{F}}) \equiv \Phi_{ji}(F) \tag{C.5}$$

which involves the dimensionless force parameter $\chi_{ij} = \chi_{ji} \ge 0$. For kinesin with a step size of $\ell = 8$ nm, the force scale $k_B T/\ell$ in (C.4) has the numerical value 0.5 pN at room temperature (corresponding to $k_B T = 4\times10^{-21}$ J).

The symmetry $\Phi_{ij}(F) = \Phi_{ji}(F)$ for the chemical transitions ensures that these latter transitions do not contribute to the sum in (C.2) and that all mechanical work is performed during the mechanical transitions. This incorporates the experimental observation in Ref. [6] that there are no mechanical substeps.

The F–dependence of the chemical transition rates can be obtained from the functional dependence of the motor velocity v on the load force F in the limit of small F. In this latter limit, the mechanical stepping transition is not rate limiting as follows from the experimental observations [6] that the stepping time, which is of the order of (or smaller than) 15 μs, is much smaller than the cycle time, which is of the order of 10 ms. Therefore, for small F, the rate limiting transitions are ATP binding, ADP release and/or P release. This can be further discriminated into two cases corresponding to small and large ATP concentration.

For small ATP concentration, ATP binding is expected to be rate limiting. Indeed, in the limit of small F and small [ATP], the 6-state model leads to the simple expression

$$v/\ell \approx \omega_{12} = 2\,\kappa_{12}\,[\mathrm{ATP}]/\left(1 + \exp[\chi_{12}\,\bar{F}]\right) \tag{C.6}$$

Exp	θ	$\chi_{12} = \chi_{45}$	$\chi_{23} = \chi_{56}$	$\chi_{34} = \chi_{61}$
[6]	0.65	0.25	0.15	0.15
[7]	0.3	0.25	0.05	0.05

TABLE II: Numerical values of the dimensionless load distribution factor θ, which determines the force dependence of the mechanical transitions, see (C.3), and of the dimensionless force parameters χ_{ij}, which govern the force dependence of the chemical transition rates, see (C.5).

for the motor velocity v where ℓ is the step size of the motor and the parametrization (C.5) has been used for $\Phi_{12}(F)$. The dimensionless force parameter χ_{12} has been determined by matching the expression (C.6) to the experimental data (i) in Fig. 2(a) with [ATP] = 10 μM as obtained by Carter and Cross in [6] and (ii) in Fig. 2(c) with [ATP] = 5 μM as measured by Visscher et al in [7].

For small load force and large ATP concentration, ADP release and/or P release should be rate limiting. The corresponding transition rates κ_{56} and κ_{61} are comparable, i.e., both for ADP release [8] and for the combined process of hydrolysis and subsequent P release [9], the literature values are in the range $100/s - 300/s$. With the simplifying assumption that the two rates are equal, i.e., that $\omega_{56} = \omega_{61}$, the 6–state model leads to the motor velocity

$$v/\ell \approx \tfrac{1}{2}\,\omega_{56} = \kappa_{56}/(1 + \exp[\chi_{56}\,\bar{F}]) \tag{C.7}$$

for small F and large [ATP]. The dimensionless force parameter $\chi_{56} = \chi_{61}$ has been determined by matching the expression (C.7) to the experimental data (i) in Fig. 2(a) with [ATP] = 1 mM [6] and (ii) in Fig. 2(c) with [ATP] = 2 mM [7].

These matching procedures lead the parameter values as shown in Table II where the force distribution factor θ has also been included.

Appendix D. 7-state model

In order to quantitatively describe the [ADP]-dependence of the motor velocity as observed by Schief et al [8], we found it necessary to include the DD state into our network description. We then obtain the extended network as shown in Fig. 5 where the DD state is labeled by $i = 7$.

In general, the 7-state model has the four additional edges $\langle 27\rangle$, $\langle 47\rangle$, $\langle 17\rangle$, and $\langle 57\rangle$ corresponding to eight forward and backward transitions. At present, the experimental data on the [ADP] and [P] dependence of the motor velocity are limited to small load forces [8] which is not sufficient to specify all eight transition rates in a unique way. For such a specification, experimental data about the functional dependence of the hydrolysis rate on load force F or on the concentrations [ATP], [ADP], and

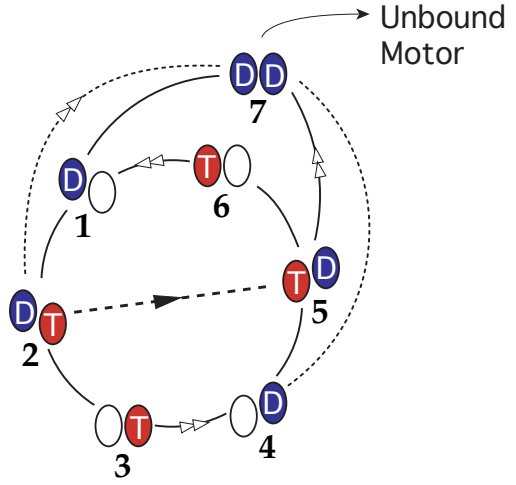

FIG. 5: 7–state model as obtained from the 6-state model in Fig. 1(c) and Fig. 4 by including the DD state with $i = 7$ and the additional edges $\langle 17\rangle$, $\langle 27\rangle$, $\langle 47\rangle$, and $\langle 57\rangle$. As in Fig. 1(c), the broken edge corresponds to the mechanical stepping transitions $|25\rangle$ and $|52\rangle$; the forward step $|25\rangle$ occurs in the direction of the black arrow. In addition, the four chemical transitions that involve ATP hydrolysis and P release are indicated by white double-arrows. In the limit of small load forces, the dynamics is dominated by the forward cycles $\mathcal{F}^+ = |12561\rangle$ and $\mathcal{F}^+_{DD} = |12571\rangle$. In this regime, we find good agreement with the experimental data if we ignore the transitions corresponding to the edges $\langle 27\rangle$ and $\langle 47\rangle$ (dotted lines) and focus on those corresponding to the edges $\langle 17\rangle$ and $\langle 57\rangle$. When calculating the average run length of the motor, it is taken to unbind only from the weakly bound state DD.

[P] would also be very valuable but such data have not been obtained so far. However, we will now argue that, in the limit of small load force F, we may ignore the four transitions represented by the two edges $\langle 47\rangle$ and $\langle 27\rangle$ or the dotted lines in Fig. 5. In this way, we arrive at a reduced 7-state model for which we obtain good agreement with all experimental data currently available.

In the limit of small load force F, the 6-state model is dominated by the forward cycle $\mathcal{F}^+$, and the probability P_4 to find the motor in the state ED with $i = 4$ is small. It is therefore plausible to ignore the flux arising from the transition $|47\rangle$. In addition, for small F, the transition rate $\omega_{25} \approx \kappa_{25}$ is several orders of magnitude larger than all other transition rates of the 6-state model, see Table I in the main text. If we assume that this property remains valid in the 7-state model, the transition probability $\pi_{25} \equiv \omega_{25}/\sum_j \omega_{2j}$ for the mechanical forward step from state DT to state TD is close to one: Once the motor has arrived in state DT with $i = 2$, it is highly likely to undergo the mechanical transition towards state TD with $i = 5$. It is then also plausible to ignore the flux arising from the transition $|27\rangle$.

Furthermore, the steady state balance conditions for the new cycles $\langle 1271\rangle$, $\langle 4574\rangle$, and $\langle 17561\rangle$, see Fig. 5, can be used in order to get some insight into the relative probabilities to leave the state DD with $i = 7$ towards the other states with $j = 1, 2, 4$, or 5. For the new cycle $\langle 1271\rangle$, the steady state balance condition is given by

$$E_{12} + E_{27} + E_{71} = \Delta\mu \tag{D.1}$$

with E_{ij} as defined in (B.1). Inserting the parametrization (A.1) for the transition rates and the expression (B.4) for the energy change $\Delta\mu$ per ATP hydrolysis, the relation (D.1) becomes

$$\frac{\kappa_{12}}{\kappa_{21}}\frac{\kappa_{27}}{\kappa_{72}}\frac{\kappa_{71}}{\kappa_{17}} = K_{\rm eq} \quad \text{for} \quad F = 0 \tag{D.2}$$

with the equilibrium constant $K_{\rm eq} \simeq 4.9 \times 10^{11}$ μM for ATP hydrolysis at room temperature. Likewise, for zero load force $F = 0$, the balance conditions for the new cycles $\langle 4574\rangle$ and $\langle 17561\rangle$ imply the relations

$$\frac{\kappa_{45}}{\kappa_{54}}\frac{\kappa_{57}}{\kappa_{75}}\frac{\kappa_{74}}{\kappa_{47}} = K_{\rm eq} \tag{D.3}$$

and

$$\frac{\kappa_{17}}{\kappa_{71}}\frac{\kappa_{75}}{\kappa_{57}}\frac{\kappa_{56}}{\kappa_{65}}\frac{\kappa_{61}}{\kappa_{16}} = 1 \tag{D.4}$$

respectively. [10]

The transition rate constants κ_{ij} have different physical dimensions $1/(\text{s}\ \mu\text{M})$ or $1/\text{s}$ depending on whether or not the corresponding transitions involve the binding of one of the chemical species. It is then more transparent to discuss the zero-force transition rates $\omega_{ij,0}$ as defined in (A.2) since all of these rates have the same physical dimension $1/\text{s}$. In terms of these zero-force rates, the three relations (D.2), (D.3), and (D.4) can be rewritten as

$$\frac{\omega_{71,0}}{\omega_{17,0}} = \frac{g_1}{[\text{ADP}][\text{P}]}\frac{\omega_{75,0}}{\omega_{57,0}} \quad \text{with} \quad g_1 \equiv \frac{\kappa_{56}}{\kappa_{65}}\frac{\kappa_{61}}{\kappa_{16}}\,, \tag{D.5}$$

$$\frac{\omega_{72,0}}{\omega_{27,0}} = \bar{g}_2\,\frac{\omega_{75,0}}{\omega_{57,0}} \quad \text{with} \quad \bar{g}_2 \equiv \frac{1}{K_{\rm eq}}\frac{\kappa_{12}}{\kappa_{21}} \tag{D.6}$$

and

$$\frac{\omega_{74,0}}{\omega_{47,0}} = \frac{g_4}{[\text{ADP}][\text{P}]}\frac{\omega_{75,0}}{\omega_{57,0}} \quad \text{with} \quad g_4 \equiv K_{\rm eq}\frac{\kappa_{54}}{\kappa_{45}}\,. \tag{D.7}$$

The three coefficients g_1, $\bar{g}_2$, and g_4 depend only on the equilibrium constant $K_{\rm eq}$ and on the rate constants of the 6-state model, which have already been determined, see Table I in the main text. Using these latter values, one obtains $g_1 \sim 10^7$ $(\mu\text{M})^2$, $\bar{g}_2 \sim 10^{-6}$, and $g_4 \sim 20$ $(\mu\text{M})^2$. These numerical values for the coefficients g_1, $\bar{g}_2$, and g_4 imply the inequalities

$$\frac{\omega_{71,0}}{\omega_{17,0}} = \frac{g_1}{g_4}\frac{\omega_{74,0}}{\omega_{47,0}} \gg \frac{\omega_{74,0}}{\omega_{47,0}} \quad \text{and} \tag{D.8}$$

$$\frac{\omega_{75,0}}{\omega_{57,0}} = \frac{1}{\bar{g}_2}\frac{\omega_{72,0}}{\omega_{27,0}} \gg \frac{\omega_{72,0}}{\omega_{27,0}}\,, \tag{D.9}$$

which indicate that, once the motor dwells in the state DD with $i = 7$, it is more likely to visit (i) the state DE with $j = 1$ rather than the state ED with $j = 4$ and (ii) the state TD with $j = 5$ rather than the state DT with $j = 2$.

If we ignore, in the limit of small load forces, the transitions corresponding to the edges $\langle 27 \rangle$ and $\langle 47 \rangle$ or the dotted lines in Fig. 5, the extension of the 6-state model to the 7-state model only involves the four additional transition rates $\omega_{17,0} = \kappa_{17}\,[ADP]$, $\omega_{71,0} = \kappa_{71}$, $\omega_{57} = \kappa_{57}$, and $\omega_{75} = \kappa_{75}\,[P]$. [1] A quantitative description of the available experimental data is obtained by the choice $\kappa_{17} = 3.23/(\mu\mathrm{M\ s})$, $\kappa_{71} = \kappa_{57} = 113/\mathrm{s}$, and $\kappa_{75} = 3.9 \times 10^{-4}/(\mu\mathrm{M\ s})$. These values of the transition rate constants have been used in order to calculate the theoretical predictions of the 7-state model as displayed by the broken lines in Fig. 3. Inspection of this figure shows that these theoretical relationships are in quantitative agreement with the experimental results.

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[1] For large concentrations, the functions $\mathcal{I}_{ij}([X])$ must saturate and attain the limiting values $\mathcal{I}_{ij}^{\infty}$. A simple parametrization that is consistent with both limits is provided by $\mathcal{I}_{ij}([X]) = \mathcal{I}_{ij}^{\infty}\, X/(\mathcal{I}_{ij}^{\infty} + X)$

[2] S. Liepelt and R. Lipowsky, Europhys. Lett. **77**, 50002 (2007)

[3] The physical interpretation of the transition energies E_{ij} is controversial, see U. Seifert, Phys. Rev. Lett. **95**, 040602 (2005) and D. Andrieux and P. Gaspard, Phys. Rev. E **74**, 011906 (2006). As explained in [2], our results are not affected by this controversy since we focus on steady state properties.

[4] The expression for $\Delta\mu$ as given by (B.4) is restricted to dilute solutions. In general, the concentrations $[X]$ have to be replaced by activities, $a_X = a_X$. The steady state balance conditions then imply $\omega_{ij,0} = \kappa_{ij}\, a_X \approx \kappa_{ij}[X]$ where the asymptotic equality applies to small $[X]$. Furthermore, comparison with (A.2) shows that $\mathcal{I}_{ij}([X]) = a_X$.

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[8] W. R. Schief, R. H. Clark, A. H. Crevenna, and J. Howard, PNAS **101**, 1183 (2004).

[9] Hackney, D. D. (2005) *Proc. Natl. Acad. Sci USA* **102**, 18338-18343

[10] For cycle $\langle 17561 \rangle$, the balance condition is given by $E_{17} + E_{75} + E_{56} + E_{61} = 0$ since this cycle involves both one ATP hydrolysis and one ATP synthesis. This also implies that the corresonding cycle flux is identically zero.