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APPENDIX A: THE ORIGIN OF D_{eff} AND τ FOR A TWO-STATE MOTOR

To see more physically how the reduction of the diffusion coefficient in (7.38) arises, consider the time derivative of the diffusion equation (7.28)

$$\partial^2 p/\partial t^2 = D\partial^2/\partial x^2(\partial p/\partial t) - v\partial/\partial x(\partial p/\partial t) - \tau\partial^3 p/\partial t^3. \qquad \text{(A1)}$$

When the probability density p is slowly varying, the third derivatives on the RHS may be neglected, in which case, using the diffusion equation (7.28), we find that

$$\partial^2 p/\partial t^2 \approx v^2\partial^2 p/\partial x^2. \qquad \text{(A2)}$$

The same result applies to the diffusion equation (6.17) for the biased random walk. It reflects the wave-like propagation of the probability-density peak at the average stepping velocity v along the motor's track, as illustrated in figure 4*a*. From (A2), one can see that the $\tau\partial^2 p/\partial t^2$ term in (7.28) therefore partially cancels the $D\partial^2 p/\partial x^2$ term, effectively reducing the diffusion coefficient D_{eff} in (7.38) from D to $D - v^2\tau$.

To understand the physical meaning of τ, consider an ensemble of two-state motors, each subjected to the same load f. The motors are either in state 1 or state 2, and, summing over all attachment sites n in (7.24) and (7.25), we may denote the probabilities for being in the two states as P_1 and P_2. It follows from (7.24) that the rate equation for P_1 is

$$dP_1/dt = k_2P_2 - k_{-2}P_1 + k_{-1}P_2 - k_1P_1 = -P_1/\tau + (k_2 + k_{-1}), \qquad \text{(A3)}$$

where we have used (7.29) together with the normalization condition $P_1+P_2 = 1$. Hence, the ensemble probabilities P_1 and P_2 approach their steady-state values with the time constant τ. At steady state, $dP_1/dt = dP_2/dt = 0$, and the average hydrolysis rate R is

$$R = k_1P_1 - k_{-1}P_2 = k_2P_2 - k_{-2}P_1, \tag{A4}$$

which together with (2.2) produces an average steady-state stepping velocity v in agreement with (7.30). Furthermore, the time derivative of (A3) yields

$$dP_1/dt + \tau d^2P_1/dt^2 = 0, \tag{A5}$$

which is what we would obtain by integrating the diffusion equation (7.28) for the probability density over all space (assuming that p and $\partial p/\partial x$ vanish asymptotically). Hence the important $\tau\partial^2 p/\partial t^2$ term in (7.28) arises from the motor's approach to steady-state stepping with the time constant τ. The one-state motor in (6.17) effectively has $\tau = 0$ and always maintains steady-state stepping, whilst the two-state motor has an internal time constant τ that introduces a time lag into the response of $\partial p/\partial t$ in (7.28). The $\tau\partial^2 p/\partial t^2$ term opposes the change in the probability density p due to the diffusion term $D\partial^2 p/\partial x^2$, and (A2) shows that at steady state it effectively reduces the diffusion coefficient in (7.38). Note that the time constant τ also gives rise mathematically to the second branch of the dispersion relation in (7.37), representing an exponential decay with a time constant that is very short compared to the time scale on which we observe diffusion (as in figure 4*a*).

APPENDIX B: THE KINETICS OF ALTERNATING HEADS

The stepping of a processive motor such as kinesin or myosin V in figure 1 requires that the two heads A and B operate alternately. The complete cycle therefore consists of two steps, first for head A and then for head B. This is particularly important if the heads are not equivalent, as occurs for some members of the kinesin superfamily (Hirokawa 1998). Hence the proper thermodynamic relation in place of (4.9) for a one-state motor with two alternating heads is

$$k_{A+}k_{B+}/k_{B-}k_{A-} = \exp[-2(\Delta G + u_0 f)/kT], \quad \text{(B1)}$$

where k_{A+} and k_{A-} are the forward and backward rate constants for head A, whilst k_{B+} and k_{B-} are the corresponding rate constants for head B. The rate equations are

$$dp_{A,n}/dt = k_{B+}p_{B,n-1} - k_{A-}p_{A,n} + k_{B-}p_{B,n+1} - k_{A+}p_{A,n}, \quad \text{(B2}a\text{)}$$

$$dp_{B,n}/dt = k_{A-}p_{A,n+1} - k_{B+}p_{B,n} + k_{A+}p_{A,n-1} - k_{B-}p_{B,n}. \quad \text{(B2}b\text{)}$$

In the continuum approximation, these equations become

$$\partial p_A/\partial t = \tfrac{1}{2}u_0^2(k_{B+} + k_{B-})\partial^2 p_B/\partial x^2 - u_0(k_{B+} - k_{B-})\partial p_B/\partial x + (k_{B+} + k_{B-})p_B - (k_{A+} + k_{A-})p_A, \quad \text{(B3}a\text{)}$$

$$\partial p_B/\partial t = \tfrac{1}{2}u_0^2(k_{A+} + k_{A-})\partial^2 p_A/\partial x^2 - u_0(k_{A+} - k_{A-})\partial p_A/\partial x + (k_{A+} + k_{A-})p_A - (k_{B+} + k_{B-})p_B. \quad \text{(B3}b\text{)}$$

Neglecting terms in $\partial^3 p/\partial x^3$ and $\partial^4 p/\partial x^4$, we find that the probability densities obey the diffusion equation (7.28), where

$$v = 2u_0(k_{A+}k_{B+} - k_{A-}k_{B-})/(k_{A+}+k_{A-}+k_{B+}+k_{B-}), \quad \text{(B4}a\text{)}$$

$$D = 2u_0^2(k_{A+}k_{B+} + k_{A-}k_{B-})/(k_{A+}+k_{A-}+k_{B+}+k_{B-}), \quad \text{(B4}b\text{)}$$

$$\tau = 1/(k_{A+}+k_{A-}+k_{B+}+k_{B-}). \quad \text{(B4}c\text{)}$$

The expressions for v, D and τ are just what we would expect from the two-state model (7.29), (7.30) and (7.31) with step size $2u_0$, together with $k_1 = k_{A+}$, $k_2 = k_{B+}$, $k_{-1} = k_{A-}$ and $k_{-2} = k_{B-}$. When the two heads are identical, $k_{A+} = k_{B+} = k_+$ and $k_{A-} = k_{B-} = k_-$, and we find that

$$D_{eff} = D - v^2\tau = \tfrac{1}{2}u_0^2(k_+ + k_-), \quad \text{(B5)}$$

which is the same result as (6.18) for the simple one-state model, where alternation of the two heads was ignored. Hence, when the two heads are identical, we may regard the motor's cycle as consisting of a single step for one head.

APPENDIX C: CALCULATION OF D_{eff} FOR A THREE-STATE MOTOR

If we look for solutions to (8.44) - (8.46) of the form $p_1 \sim \exp[i(kx - \omega t)]$, *etc.*, then it follows that

$$[i\omega - (k_1 + k_{-3})][i\omega - (k_{-1} + k_2)][i\omega - (k_{-2} + k_3)] - k_2k_{-2}[i\omega - (k_1 + k_{-3})]$$

$$- k_1k_{-1}[i\omega - (k_{-2} + k_3)] + k_{-3}k_{-2}k_{-1}(1 + u_0ik - \tfrac{1}{2}u_0^2k^2) + k_1k_2k_3(1 - u_0ik - \tfrac{1}{2}u_0^2k^2)$$

$$- k_3k_{-3}[i\omega - (k_{-1} + k_2)](1 - u_0ik - \tfrac{1}{2}u_0^2k^2)(1 + u_0ik - \tfrac{1}{2}u_0^2k^2) = 0. \quad \text{(C1)}$$

Neglecting terms in ω^3 and k^4, we find that

$$\omega^2(k_1+k_{-1}+k_2+k_{-2}+k_3+k_{-3}) + i\omega[k_1(k_2+k_{-2}+k_3) + k_{-3}(k_{-1}+k_2+k_{-2}) + k_{-1}(k_{-2}+k_3) + k_2k_3]$$

$$- u_0ik(k_1k_2k_3-k_{-3}k_{-2}k_{-1}) - \tfrac{1}{2}u_0^2k^2(k_1k_2k_3+k_{-3}k_{-2}k_{-1}) = 0. \quad \text{(C2)}$$

To determine the effective diffusion coefficient D_{eff}, we look for solutions that satisfy the dispersion relation (7.36) in the limit of small ω and k. Substituting $kv - iD_{eff}k^2$ for ω in (C2) and keeping terms of $O(k^2)$, we find

$$k^2v^2(k_1+k_{-1}+k_2+k_{-2}+k_3+k_{-3}) + i(kv - iD_{eff}k^2)[k_1(k_2+k_{-2}+k_3) + k_{-3}(k_{-1}+k_2+k_{-2}) + k_{-1}(k_{-2}+k_3) + k_2k_3]$$

$$- u_0ik(k_1k_2k_3-k_{-3}k_{-2}k_{-1}) - \tfrac{1}{2}u_0^2k^2(k_1k_2k_3+k_{-3}k_{-2}k_{-1}) = 0. \quad \text{(C3)}$$

This equation must be true for all k (in the limit where $k \rightarrow 0$). Hence, setting the coefficients of k and k^2 equal to zero, we find that the average stepping velocity is

$$v = u_0(k_1k_2k_3-k_{-3}k_{-2}k_{-1})/[k_1(k_2+k_{-2}+k_3)+k_{-3}(k_{-1}+k_2+k_{-2})+k_{-1}(k_{-2}+k_3)+k_2k_3], \quad \text{(C4)}$$

whilst the diffusion coefficient D_{eff} for the three-state model is given by

$$D_{eff} = [\tfrac{1}{2}u_0^2(k_1k_2k_3+k_{-3}k_{-2}k_{-1})-v^2(k_1+k_{-1}+k_2+k_{-2}+k_3+k_{-3})]/[k_1(k_2+k_{-2}+k_3)$$

$$+k_{-3}(k_{-1}+k_2+k_{-2})+k_{-1}(k_{-2}+k_3)+k_2k_3].$$

$$\text{(C5)}$$

Note that the randomness for the three-state model from (7.39), (C4) and (C5) may be written as

$$r = [u_0^2(k_1k_2k_3+k_{-3}k_{-2}k_{-1})-2v^2(k_1+k_{-1}+k_2+k_{-2}+k_3+k_{-3})]/u_0^2(k_1k_2k_3-k_{-3}k_{-2}k_{-1}). \quad \text{(C6)}$$

When backward transitions are neglected, $k_{-1} = k_{-2} = k_{-3} = 0$, and we find that

$$r = [k_1^2k_2^2 + k_1^2k_3^2 + k_2^2k_3^2]/[k_1k_2+ k_1k_3+k_2k_3]^2, \quad \text{(C7)}$$

in agreement with the theory of Svoboda *et al*. (1994).