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Periodic sequential kinetic models with jumping, branching and deaths

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Abstract

Motivated by recent applications to experiments on processive molecular motors (i.e., protein molecules that drag loads along linear, periodic molecular filaments), the analysis of Derrida (J. Stat. Phys. 31 (1983) 433–450) is extended to obtain exact, closed form expressions for the velocity, V, and dispersion (or diffusion constant), D, of discrete one-dimensional nearest-neighbor kinetic hopping models with arbitrary forwards and backwards periodic rate constants of general period N, which include, in addition: (i) direct jumps between sites, $l = kN$ ($k = 0, \pm 1, \ldots$) and sites $(k \pm 1)N$; (ii) the possibility of finite, periodically arranged, but otherwise arbitrary, side branches at *each* site l; and (iii) an arbitrary (but periodic) probability rate of death at each site (which describes the motor protein detaching from the track). General expressions, following from previously developed theoretical principles, are given for the forces predicted by the corresponding extended motor models. The results are illustrated by plots of "randomness" ($\propto D/V$) for more-or-less realistic $N = 2$ molecular-motor models as a function of the load force, F.

Dedicated to Joel L. Lebowitz with admiration and affection

1. Introduction and summary

Problems concerning the molecular basis of biological motion and transport (see, e.g., Refs. [1,2]) have recently attracted increased theoretical attention [3–14] stimulated, in particular, by striking experiments [15–19] in which a *single* motor protein molecule — such as kinesin [1,2,15–17] — is observed in vitro to move stochastically along a linear molecular track — a microtubule in the case of kinesin. Such molecular motors are, typically, powered by ATP (adenosine triphosphate [1,2]); they move with mean velocities, V, up to 1000 nm/s [19] and may exert forces of 5 or 6 pN, or more [18,19] on biological vesicles, in vivo [1,2], or silica beads, etc., in vitro [15–17]. Since the motion is stochastic, the location, $x(t)$, at time t of a motor initially bound at a site

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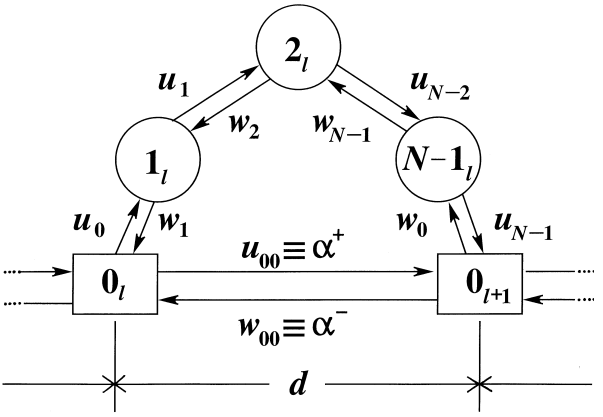

Fig. 1. Representation of the basic N-state periodic sequential kinetic scheme with forward and backward rates u_j and w_j $(j=0,1,\ldots,N-1)$ between states 0_l, $1_l,\ldots,(N-1)_l$, at lattice site l and state $N_l \equiv 0_{l+1}$ at site $l+1$, etc., *supplemented* by direct forward and backward *jumps* from states 0_l to $0_{l\pm1}$, with rates $u_{00} \equiv \alpha^+$ and $w_{00} \equiv \alpha^-$, respectively. When regarded as a one-dimensional lattice hopping model, successive sites $l, l+1,\ldots$ (in states $0_l, 0_{l+1},\ldots$) are spaced at separations $\Delta x = d$ along the x-axis, while the successive intermediate ("internal motor") states $j_l,(j+1)_l,\ldots$, may be regarded as separated by uniform spaces $\Delta x_1 = d/N$.

on the molecular track at $x=0$, is subject to variation: the variance of $x(t)$ may also be observed [15,19] and can be encapsulated in a *dispersion*, or effective diffusion constant, D [15,4,8,9]. The dependence of both V and D on the load, F, and on the power supply (measured, e.g., by the concentration, [ATP]) can be studied in vitro [15–19].

The simplest theoretical models, appropriate to periodic molecular tracks (such as microtubules) with sites at $x = ld$ $(l=0,\pm1,\pm2,\ldots)$, postulate a sequence of N discrete "internal" states, $j=0,1,\ldots,N-1, N \equiv 0$, of a motor protein, linked together dynamically by a sequential (or one-dimensional) kinetic scheme: see Fig. 1 in the special case of vanishing "jumping" rates, i.e., with $u_{00} = w_{00} = \alpha^{\pm} \equiv 0$ [7–10]. After passing "processively" through kN states $(k=1,2,\ldots)$, say from state j_l ("at" site l) to state j_{l+k} ("at" site $l+k$), the motor has moved a distance $\Delta x = kd$ along the track Fig. 1. More elaborate "thermal ratchet" models, in which the molecular motor is viewed as a Brownian particle switching stochastically between continuous, one-dimensional periodic but asymmetric potentials [6,9,14], have also been studied; in addition, the extension of the kinetic schemes to allow for *waiting-time distributions* has also been considered [10,11].

The current theoretical models give reasonable semi-quantitative descriptions of motor protein motion. However, these theories neglect some potentially significant features such as (i) detachment or "death," in which the motor irreversibly unbinds from the molecular track; (ii) the possible existence of branching biochemical motor states that lead off the main processive sequence; and (iii) the random "jumping", or diffusion, of a molecular motor along the track in the absence of a power source (or, e.g., without using the ATP hydrolysis cycle). All of these features have been observed

experimentally [17–19], but they have not so far been addressed theoretically in a systematic way.

In an effort to repair these omissions, we present here analyses of three extensions of the basic *periodic sequential kinetic scheme* sketched above (and embodied in Fig. 1 when $\alpha^{\pm} \equiv 0$). Note first, however, that if, for simplicity, we associate the elementary internal motor transitions ($j \to j+1$) with equal *spatial* increments $\Delta x_1 = d/N$ (so that in a full cycle, ($j \to j+N$), the motor advances through the "stepping distance," d, separating adjacent sites on the molecular track), then the basic kinetic scheme reduces to a *periodic hopping model* on a uniform one-dimensional lattice with (nonnegative) nearest-neighbor forward and backward rate parameters

$$u_j \equiv u_{j\pm N}, \qquad w_j \equiv w_{j\pm N}\ ; \tag{1}$$

see Fig. 1 with $\alpha^{\pm} \equiv 0$. Such models have been investigated in the past with the primary aim of attacking the more difficult problems of diffusion and random walks in *random media*: see, e.g., [20,21] and, for some more recent developments, [22]. But, as noted recently [9], the seminal analysis of Derrida [20] in 1983 already provides precisely what is needed in the context of molecular motors, namely, formally exact and explicit expressions for the asymptotic (long time) drift velocity

$$V_0 = V_0(\{u_j, w_j\}) = \lim_{t\to\infty} \frac{\mathrm{d}}{\mathrm{d}t}\langle x(t)\rangle\ , \tag{2}$$

and dispersion (or diffusion constant)

$$D_0 = D_0(\{u_j, w_j\}) = \tfrac{1}{2}\lim_{t\to\infty} \frac{\mathrm{d}}{\mathrm{d}t}[\langle x^2(t)\rangle - \langle x(t)\rangle^2]\ , \tag{3}$$

where, again, $x(t)$ represents the spatial displacement along the motor track.

The first (and simplest) extension of the basic periodic sequential kinetic scheme we consider is that shown in Fig. 1: parallel jumping rates, $u_{00} = \alpha^{+}$ (forwards) and $w_{00} = \alpha^{-}$ (backwards) allow for drift and diffusion from site to site along the molecular track even if the processive sequence is "switched off", e.g., by setting $u_0 = w_0 = 0$. Fig. 2 generalizes the basic scheme by allowing a finite side-branch process to spring from each primary motor state j with "outward" rates $\beta_{j,i} \equiv \beta_{j\pm N,i}$ ($i = 0, 1, \ldots, L-1$) and "inward" rates $\gamma_{j,i} \equiv \gamma_{j\pm N,i}$ ($i = 1, 2, \ldots, L$). For notational convenience we take all side branches to be of length L: but if some branches are shorter one need only set the appropriate rates, say β_{j,L_j}, to zero. Multiple branches and branched branches, or trees, can easily be handled by the methods described below (in Section 3). Finally, the extended scheme illustrated in Fig. 3 allows for detachment of the motor protein from the track by introducing a specific death rate, $\delta_j \equiv \delta_{j\pm N}$, for each motor state j.

For all these three general kinetic schemes we have obtained explicit expressions for the velocities V_α, V_β, and V_δ, and for the dispersions, D_α, D_β, and D_δ, by extending the original method devised by Derrida [20]. Of course, when the extra rates, which we denote collectively by α, β, γ and δ, vanish, Derrida's original results are recaptured in all cases. *Compound models* that combine, e.g., jumping and branching, can be analyzed in a precisely parallel way in order to compute $V_{\alpha\beta}$ and $D_{\alpha\beta}$, etc. It is also worth recalling that Derrida's method extends (although with greater complications)

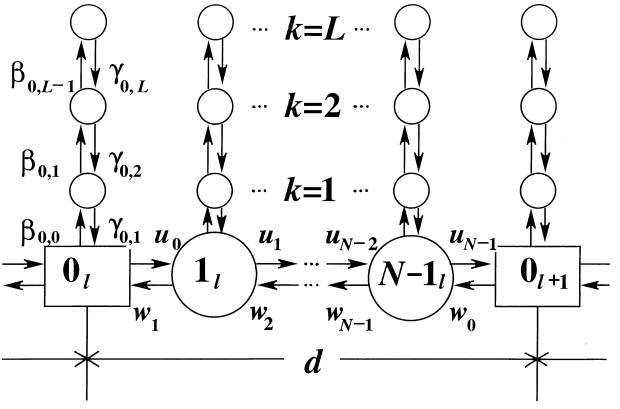

Fig. 2. Depiction of the basic N-state periodic sequential kinetic scheme, as shown in Fig. 1 (with $\alpha^{\pm} \equiv 0$) with states $0_l, 1_l, \ldots,$ which can be regarded as carrying a label $k = 0$, *supplemented* by *side branches* with outwards and inwards rates $\beta_{j,k} \equiv \beta_{j+N,k}$ and $\gamma_{j,k} \equiv \gamma_{j+N,k}$ between branch states $(j,k)_l$ with $k = 1, 2, \ldots, L$.

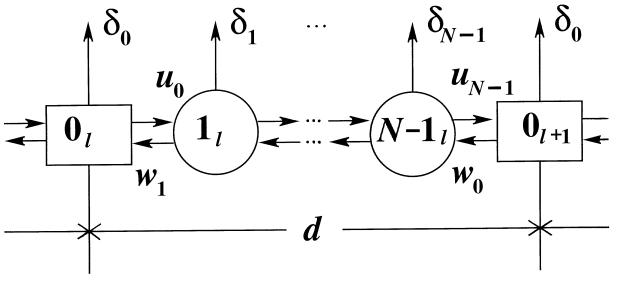

Fig. 3. Representation of an N-state periodic sequential kinetic scheme with periodic but otherwise arbitrary death rates, $\delta_j \geqslant 0$, present at each site, so modeling the stochastic detachment of a motor protein from its molecular track.

to higher-order long-time moments of $x(t)$ [20]. For ease of reference we report our main velocity and diffusion results in this Section and present the detailed derivations in Sections 2–4.

To apply any kinetic scheme as a model of a molecular motor one needs theoretical principles relating the kinetics to the forces exerted and to any external loads imposed. The authors have recently expounded a general theory [10,11] to answer this need. The principal results of that approach for the extended kinetic schemes considered here are presented in Section 5. In addition, as an illustration, the explicit application of the results to some $(N = 2)$-state models that roughly describe real motor protein systems, is sketched.

To present our expressions for V and D we note, first, that they depend algebraically *only* on *linear sequential products of rate ratios* (which might be regarded, chemically, as pseudo partial equilibrium constants for intermediate reactions or subprocesses). Specifically, for the model with jumping it is sufficient to consider only the two types

of product

$$\Pi_j^k \equiv \prod_{i=j}^{k} \frac{w_i}{u_i} \quad \text{and} \quad \Pi_j^{\dagger k} \equiv \prod_{i=j}^{k} \frac{w_{i+1}}{u_i} = \frac{w_{k+1}}{w_j}\Pi_j^k \,. \tag{4}$$

The branching scheme requires, in addition, the branch products

$$\Pi_j^{\beta,k} \equiv \prod_{i=1}^{k} \frac{\beta_{j,i-1}}{\gamma_{j,i}} \,. \tag{5}$$

For the model with deaths one needs the analogs of (4), which we will call $\widetilde{\Pi}_j^k$ and $\widetilde{\Pi}_j^{\dagger,k}$, that are obtained by replacing u_j and w_j by the "renormalized" values

$$\tilde{u}_j = u_j\varphi_{j+1}/\varphi_j \quad \text{and} \quad \widetilde{w}_j = u_j\varphi_{j-1}/\varphi_j \,, \tag{6}$$

where the renormalization coefficients, $\varphi_j \equiv \varphi_{j\pm N}$ $(j=0,1,\ldots,N-1)$, are conveniently normalized by

$$\varphi_0 \equiv 1 \,. \tag{7}$$

Specifically, the φ_j are the components of the right eigenvector, $\boldsymbol{\varphi} = [\varphi_j]$, associated with the eigenvalue $\lambda = \lambda(\{u_j, w_j\})$ of smallest magnitude of the $N \times N$ rate matrix $\mathbf{M}[\{u_j, w_j; \delta_j\}]$ with the nonzero elements

$$M_{j,j-1} = -w_j, \qquad M_{j,j} = u_j + w_j + \delta_j, \qquad M_{j,j+1} = -u_j \,, \tag{8}$$

where the periodicity (1) should be recalled so that, in particular,

$$M_{0,-1} \equiv M_{0,N-1} = -w_0 \quad \text{and} \quad M_{N-1,N} \equiv M_{N-1,0} = -u_{N-1} \,. \tag{9}$$

Thus $\mathbf{M}$ is close to tridiagonal but has nontrivial corner elements on the counter diagonal. Since $\boldsymbol{\varphi}$ is defined via $\mathbf{M}\boldsymbol{\varphi} = \lambda\boldsymbol{\varphi}$, the determination of the φ_j requires, in general, solution of the Nth order algebraic equation $|\mathbf{M} - \lambda\mathbf{I}| = 0$: but for certain special cases (such as when the rates take values $u_<$, $w_<$ and $\delta_<$ for $0 \leqslant j < j^\dagger$ and conversely for $j^\dagger \leqslant j < N-1$) explicit analytical results may be obtained. Note that $\mathbf{M}$ is stochastic when $\delta = 0$ (in the sense that the row sums then vanish identically).

1.1. Hopping with jumps

For the basic kinetic scheme supplemented by jumps from states 0_l to states $0_{l\pm1}$ (see Fig. 1), the drift velocity may now be written as

$$V_\alpha = V_0 + V_1(\alpha^\pm) \,, \tag{10}$$

$$V_0 = d(1 - \Pi_1^N)/R_N, \qquad V_1 = d(\alpha^+ - \alpha^-)r_0/R_N \,, \tag{11}$$

where, using the notations above,

$$R_N = \sum_{j=0}^{N-1} r_j, \qquad r_j = u_j^{-1}\left[1 + \sum_{k=1}^{N-1} \Pi_{j+1}^{j+k}\right] \,. \tag{12}$$

Note that V_0 in (11) is just Derrida's original expression for the mean velocity [20]. The dispersion may, similarly, be decomposed as

$$D_\alpha = D_{0,\alpha} + D_1(\alpha^\pm) + D_2(\alpha^\pm)\,, \tag{13}$$

with a primary contribution, surviving when $\alpha^+ = \alpha^- = 0$, of

$$D_{0,\alpha} = (d/N)\{[V_\alpha S_N + dU_N]/(R_N)^2 - \tfrac{1}{2}(N+2)V_0\}(V_\alpha/V_0)\,, \tag{14}$$

$$S_N = \sum_{j=0}^{N-1} s_j \sum_{k=0}^{N-1}(k+1)r_{k+j+1}, \qquad U_N = \sum_{j=0}^{N-1} u_j r_j s_j\,, \tag{15}$$

in which, recalling (4), the new sum is given by

$$s_j = u_j^{-1}\left[1 + \sum_{k=1}^{N-1} \Pi_{j-1}^{\dagger j-k}\right]\,. \tag{16}$$

Setting $V_\alpha = V_0$ in (14) reproduces Derrida's result for the dispersion [20]. The symmetric jump contribution to D_α is simply

$$D_1(\alpha^\pm) = \tfrac{1}{2}d^2(\alpha^+ + \alpha^-)r_0/R_N\,, \tag{17}$$

while the antisymmetric part, vanishing when $\alpha^+ = \alpha^-$, is

$$D_2(\alpha^\pm) = d^2(\alpha^+ - \alpha^-)\{[V_\alpha J_0 - dJ_1]/V_0 R_N - \tfrac{1}{2}(N-2)r_0\}/NR_N\,, \tag{18}$$

where the further sums required are

$$J_0 = r_0 \sum_{j=0}^{N-1} j s_j - u_0^{-1} \sum_{j=0}^{N-1}(j+1)\left[r_{j+1} + \sum_{k=1}^{N-1} r_{j+k+1}\Pi_1^k\right]\,, \tag{19}$$

$$J_1 = r_0 + \sum_{j=1}^{N-1} r_j \Pi_1^j + (\alpha^+ - \alpha^-)\frac{r_0}{u_0}\sum_{j=1}^{N-1} j\Pi_1^j\,. \tag{20}$$

We may, finally, remark that, with obvious changes, these results adapt immediately to jumps from motor state j_l to $j_{l\pm1}$ for any j. Further sets of parallel jumps can also be handled: in the expression for V_α they lead to further additive terms like V_1 in (11).

1.2. Hopping with branches

For the branching kinetic scheme specified in Fig. 2 the velocity is given by

$$V_\beta(\beta,\gamma) = d(1 - \Pi_1^N)/R_N^\beta\,, \tag{21}$$

which is identical to Derrida's result, namely V_0 in (11), except for the modified sum

$$R_N^\beta = \sum_{j=0}^{N-1} r_j^\beta, \qquad r_j^\beta = r_j\left[1 + \sum_{k=1}^{L} \Pi_j^{\beta,k}\right]\,, \tag{22}$$

where the definitions (5) and (12) should be recalled. The dispersion can be written as

$$D_\beta(\beta,\gamma) = D_{0,\beta}(\beta,\gamma) + D_{1,\beta}(\beta,\gamma) \tag{23}$$

with the primary term, that survives even when all the $\beta_{j,i}$ vanish, given by

$$D_{0,\beta} = (d/N)\{[V_\beta S_N^\beta + dU_N^\beta]/(R_N^\beta)^2 - \tfrac{1}{2}(N+2)V_\beta\}\,, \tag{24}$$

where the sums, closely analogous to S_N and U_N in (15), are

$$S_N^\beta = \sum_{j=0}^{N-1} s_j^\beta \sum_{k=0}^{N-1}(k+1) r_{k+j+1}^\beta, \qquad U_N^\beta = \sum_{j=0}^{N-1} u_j r_j s_j^\beta\,, \tag{25}$$

in which, in analogy to (16), we have

$$s_j^\beta = u_j^{-1}\left[1 + \sum_{l=1}^{L} \Pi_j^{\beta,l} + \sum_{k=1}^{N-1}\left(1 + \sum_{l=1}^{L}\Pi_{j-k}^{\beta,l}\right)\Pi_{j-k}^{\dagger j-1}\right]\,. \tag{26}$$

The contribution due purely to the branching is

$$D_{1,\beta} = V_\beta^2 \sum_{j=0}^{N-1}\sum_{k=1}^{L} J_{j,k}^\beta\,, \tag{27}$$

with coefficients, vanishing when the $\beta_{j,i}$ vanish, given by

$$J_{j,k}^\beta = -\frac{r_j}{R_N^\beta \gamma_{j,k}}\left[\sum_{l=k}^{L}\Pi_j^{\beta,l} + \sum_{i=1}^{k-1}\frac{\beta_{j,i}}{\beta_{j,0}}\Pi_j^{\beta,i}\sum_{l=k-i}^{L}\Pi_j^{\beta,l}\right]\,. \tag{28}$$

1.3. Hopping with deaths

One must now compute the renormalization factors defined in (7)–(9) above and, thence, the renormalized rate factors $\tilde{u}_j$ and $\widetilde{w}_j$ given in (6). The mean velocity is then given by

$$V_\delta = d(1 - \widetilde{\Pi}_1^N)/\tilde{R}_N\,, \tag{29}$$

where $\widetilde{\Pi}_1^N$, $\tilde{R}_N$, and the $\tilde{r}_j$ are defined, using $\tilde{u}_j$ and $\widetilde{w}_j$, in precise analogy to (4) and (12). Likewise, the dispersion is given by

$$D_\delta = (d/N)\{[V_\delta \tilde{S}_N + d\widetilde{U}_N]/(\tilde{R}_N)^2 - \tfrac{1}{2}(N+2)V_\delta\}\,, \tag{30}$$

where $\tilde{S}_N$, $\widetilde{U}_N$, and $\tilde{s}_j$ are defined, similarly, in precise analogy to (15) and (16).

For the general ($N=2$)-state model with death rates δ_0 and δ_1 the φ_j are readily found and, recalling convention (7), the velocity and dispersion may be written explicitly as

$$V_\delta = d(u_0u_1 - w_0w_1)\varphi_1(u,w,\delta)/\Delta_1(u,w;\varphi_1)\,, \tag{31}$$

$$D_\delta = \tfrac{1}{2}d^2[(u_0u_1 + w_0w_1)\varphi_1 - 2\varphi_1(V_\delta/d)^2]/\Delta_1\,, \tag{32}$$

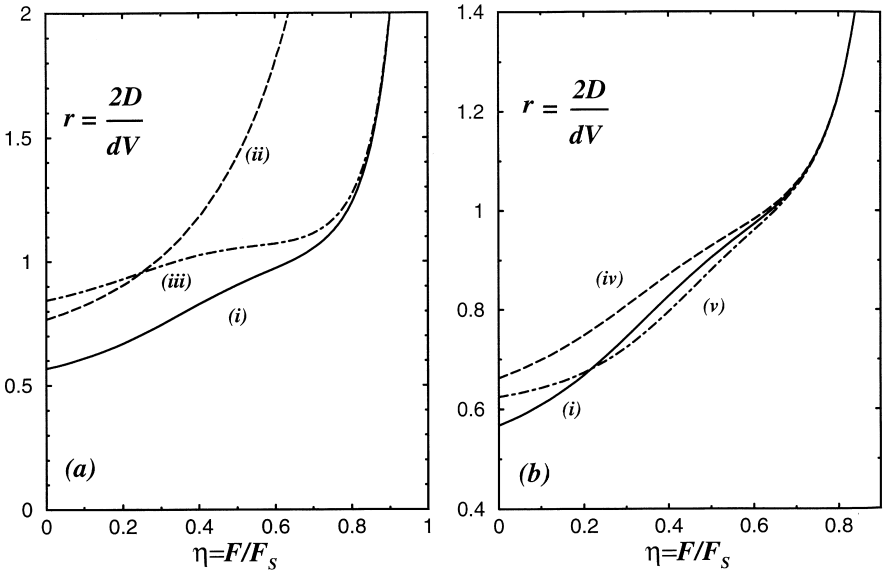

Fig. 4. Variation of the dimensionless "randomness" parameter, $r = 2D/dV$, for particular $(N = 2)$-state model motor proteins as a function of the load force, $F = \eta F_S$, relative to the stalling force, F_S, at which the velocity, $V(F)$, goes to zero. The bold curves labeled (i) in parts (a) and (b) correspond to a simple, unmodified sequential model with moderately realistic rates u_0, u_1, w_0 and w_1 and "load distribution factors" (see Refs. [10,11]) $\theta_0^+ = \theta_1^+ = 0$, $\theta_0^- = \theta_1^- = 0.5$: see Table 1 (and model (d) in Refs. [10,11]). In plot (ii) direct jumps, with $\alpha^+ = \alpha^-$, have been incorporated, while in (iii) a side branch process of length $L_1 = 1$ has been introduced in motor state $j = 1$. The effects of (iv) a death rate from state $j = 0$ only and (v) from state $j = 1$ only, are illustrated in (b); note the change of scales from (a). The specific parameters for cases (i)-(v) are given in Table 1.

with the auxiliary functions given by

$$\Delta_1 \equiv (u_0 + w_0)\varphi_1^2 + u_1 + w_1 \,, \tag{33}$$

$$\varphi_1 = \tfrac{1}{2}(u_0 + w_0)^{-1}[u_0 + w_0 + \delta_0 - u_1 - w_1 - \delta_1 + \sqrt{\Delta}] \,, \tag{34}$$

$$\Delta = (u_0 + w_0 + \delta_0 - u_1 - w_1 - \delta_1)^2 + 4(u_0 + w_0)(u_1 + w_1) \,. \tag{35}$$

An application of these specific results is illustrated in Fig. 4.

2. Periodic kinetics with jumping

In this section we consider the general periodic sequential kinetic model with jumps as described in Fig. 1. The probability $P_j(l,t)$ of finding the motor at site l in state j at time t satisfies the master equation

$$\frac{\mathrm{d}}{\mathrm{d}t}P_j(l,t) = u_{j-1}P_{j-1}(l,t) + w_{j+1}P_{j+1}(l,t) - (u_j + w_j)P_j(l,t) \,, \tag{36}$$

for $j \neq 0$, while for $j = 0$ one must include the jumping rates so that

$$\frac{\mathrm{d}}{\mathrm{d}t}P_0(l,t) = u_{N-1}P_{N-1}(l-1;t) + w_1P_1(l,t) + \alpha^+P_0(l-1;t) + \alpha^-P_0(l+1;t) - (u_0 + w_0 + \alpha^+ + \alpha^-)P_0(l,t)\,. \tag{37}$$

Recall that, because of the periodicity, the state N_l coincides with 0_{l+1}. Without loss of generality, for the present purposes, we may assume that the initial condition is $P_j(l;0) = P_j^0\delta_{l,0}$. Conservation of probability then requires

$$\sum_{l=-\infty}^{+\infty}\sum_{j=0}^{N-1} P_j(l,t) = 1 \quad \text{for all } t\,, \tag{38}$$

where, here and below, we see that $P_j(l,t)$ approaches zero rapidly when $l \to \pm\infty$ at fixed $t \geqslant 0$ for all j.

Following Derrida's approach closely [20], we now define two auxiliary functions for each state j, namely,

$$B_j(t) \equiv \sum_{l=-\infty}^{+\infty} P_j(l,t), \qquad C_j(t) \equiv \sum_{l=-\infty}^{+\infty} (j+Nl)P_j(l,t)\,. \tag{39}$$

The master equations (36) and (37) then yield

$$\frac{\mathrm{d}}{\mathrm{d}t}B_j(t) = u_{j-1}B_{j-1} + w_{j+1}B_{j+1} - (u_j + w_j)B_j \tag{40}$$

which is valid for *all* j since the $j = 0$ terms containing α^+ and α^- cancel in the summation on l. Similarly, for $j \neq 0$ we obtain

$$\frac{\mathrm{d}}{\mathrm{d}t}C_j(t) = u_{j-1}C_{j-1} + w_{j+1}C_{j+1} - (u_j + w_j)C_j + u_{j-1}B_{j-1} - w_{j+1}B_{j+1}\,, \tag{41}$$

while for $j = 0$ the result is

$$\frac{\mathrm{d}}{\mathrm{d}t}C_0(t) = u_{N-1}C_{N-1} + w_1C_1 - (u_0 + w_0)C_0 + u_{N-1}B_{N-1} - w_1B_1 + (\alpha^+ - \alpha^-)NB_0\,. \tag{42}$$

Now it is heuristically clear that for *fixed finite* N, the behavior of $P_j(l,t)$ at large times should describe a packet of probability density moving with a steady drift velocity, V, and broadening diffusively. This conclusion may be demonstrated generally with the aid of a matrix formulation in which a Fourier-space ($x \Rightarrow q$) representation is utilized (see, e.g., Ref. [23]). With this picture in mind we introduce (again following Derrida [20]) the ansatz

$$B_j(t) \to b_j, \quad C_j(t) - a_jt \to T_j \tag{43}$$

which should be valid for suitable constants b_j, a_j and T_j, which we will determine, when $t \to \infty$. Note that periodicity implies

$$b_{j+N} = b_j, \quad a_{j+N} = a_j, \quad \text{and} \quad T_{j+N} = T_j\,. \tag{44}$$

Then from (40) with $dB_j/dt = 0$ we may conclude

$$f_{j+1} \equiv w_{j+1}b_{j+1} - u_j b_j = w_j b_j - u_{j-1}b_{j-1} \equiv f_j \,. \tag{45}$$

By iteration one sees that $f_{j+1} = f_0$ must be constant which leads to

$$b_j = -\frac{f_0}{u_j} + \frac{w_{j+1}}{u_j}b_{j+1} = -\frac{f_0}{u_j}\left[1 + \frac{w_{j+1}}{u_{j+1}}\right] + \frac{w_{j+1}w_{j+2}}{u_j u_{j+1}}b_{j+2} = \cdots \,. \tag{46}$$

After $N-1$ steps we may use (44), i.e., $b_{j+N} = b_j$. Then, noting that the normalization condition (38) yields $\sum_{j=0}^{N-1} b_j = 1$, enables us to conclude

$$b_j = \frac{r_j}{R_N} \quad \text{with} \quad r_j = \frac{1}{u_j}\left[1 + \sum_{k=1}^{N-1} \Pi_{j+1}^{j+k}\right] \,, \tag{47}$$

where the notations in (4) and (12) have been invoked.

To determine the coefficients a_j and T_j in (43) we use (41) and (42): the secular term, $C_j \approx a_j t$, imposes the condition

$$w_{j+1}a_{j+1} - u_j a_j = w_j a_j - u_{j-1}a_{j-1} \quad (\text{all } j) \,, \tag{48}$$

while the "phase shifts" T_j must satisfy

$$a_j = [u_{j-1}T_{j-1} + w_{j+1}T_{j+1} - (u_j + w_j)T_j] + u_{j-1}B_{j-1} - w_{j+1}B_{j+1} \,, \tag{49}$$

for $j \neq 0$ but with, for $j = 0$,

$$a_0 = [u_{N-1}T_{N-1} + w_1 T_1 - (u_0 + w_0)T_0] + u_{N-1}B_{N-1} - w_1 B_1 + (\alpha^+ - \alpha^-)NB_0 \,. \tag{50}$$

Comparing (48) with (45) we conclude

$$a_j = Ab_j \,, \tag{51}$$

where, since $\sum_{j=0}^{N-1} b_j = 1$, the constant A can be found by summing the a_j and using (49) and (50): the T_j then cancel identically to yield

$$A = \sum_{j=0}^{N-1} a_j = \sum_{j=0}^{N-1}(u_j - w_j)b_j + (\alpha^+ - \alpha^-)Nb_0 \,. \tag{52}$$

On substituting result (47) for b_j one finds that all the intermediate products cancel in the summation leaving the simple result

$$A = N[1 - \Pi_1^N + (\alpha^+ - \alpha^-)r_0]/R_N \,, \tag{53}$$

where we may note that $\Pi_0^{N-1} \equiv \Pi_1^N$.

In order to find the T_j we introduce (following Derrida [20])

$$y_j \equiv w_{j+1}T_{j+1} - u_j T_j \,, \tag{54}$$

and rewrite (49) and (50) as

$$y_j - y_{j-1} = a_j - u_{j-1}b_{j-1} + w_{j+1}b_{j+1} \quad \text{for} \quad j \neq 0 \,, \tag{55}$$

$$y_0 - y_{N-1} = a_0 - u_{N-1}b_{N-1} + w_1 b_1 - (\alpha^+ - \alpha^-)Nb_0 \quad \text{for} \quad j = 0 \,. \tag{56}$$

These equations can be solved along the lines used to treat (45) which yield

$$y_j = j(\alpha^+ - \alpha^-)b_0 + u_j b_j + (A/N)\sum_{i=0}^{N-1}(i+1)b_{j+i+1} + c\,, \tag{57}$$

where c is an arbitrary constant which, it transpires, cancels in the final expression for the dispersion, D. One can check that this form solves (55) and (56) with the help of the relation

$$u_j b_j - w_{j+1}b_{j+1} = A/N - (\alpha^+ - \alpha^-)b_0 \tag{58}$$

which follows from (52) and (47). Iterating (54) yields

$$T_j = -\frac{y_j}{u_j} + \frac{w_{j+1}}{u_j}T_{j+1} = -\frac{y_j}{u_j} - \frac{w_{j+1}y_{j+1}}{u_j u_{j+1}} + \frac{w_{j+1}w_{j+2}}{u_j u_{j+1}}T_{j+2} = \cdots\,. \tag{59}$$

Invoking the periodicity (44) then leads to [20]

$$T_j = -\frac{1}{u_j}\left[y_j + \sum_{k=1}^{N-1} y_{j+k}\Pi_{j+1}^{j+k}\right]/(1-\Pi_1^N)\,. \tag{60}$$

To calculate the drift velocity V_α and the diffusion constant D_α we use the general definitions adopted in (2) and (3). Clearly, one has

$$\langle x(t)\rangle = \frac{d}{N}\sum_{l=-\infty}^{+\infty}\sum_{j=0}^{N-1}(j+Nl)P_j(l,t) = \frac{d}{N}\sum_{j=0}^{N-1}C_j(t)\,, \tag{61}$$

from which, using (36) and (37), we find

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}\langle x(t)\rangle &= \frac{d}{N}\sum_{l=-\infty}^{+\infty}\sum_{j=0}^{N-1}(j+Nl)[u_{j-1}P_{j-1}(l,t)+w_{j+1}P_{j+1}(l,t)-(u_j+w_j)P_j(l,t)]\\ &\quad + \frac{d}{N}\sum_{l=-\infty}^{+\infty}Nl[\alpha^+P_0(l-1;t)+\alpha^-P_0(l+1;t)-(\alpha^+-\alpha^-)P_0(l,t)]\\ &= \frac{d}{N}\sum_{j=0}^{N-1}(u_j-w_j)B_j(t) + \frac{d}{N}(\alpha^+-\alpha^-)NB_0(t)\,.\end{aligned} \tag{62}$$

When $t\to\infty$ this reduces, with the aid of (52) to

$$\lim_{t\to\infty}\frac{\mathrm{d}}{\mathrm{d}t}\langle x(t)\rangle = \frac{d}{N}\left[\sum_{j=0}^{N-1}(u_j-w_j)b_j + (\alpha^+-\alpha^-)Nb_0\right] = \frac{d}{N}A\,. \tag{63}$$

Finally, using (2) and result (53) we can express the drift velocity as

$$V_\alpha = d[1-\Pi_1^N + (\alpha^+-\alpha^-)r_0]/R_N\,. \tag{64}$$

This can be rewritten as a sum of two terms, as in (10) and (11), where the first term, $V_0(u,w)$, is independent of the jumping rates, $\alpha^\pm$, and corresponds precisely to Derrida's original model. The second term allows for the possibility of direct jumps over a full period. As remarked in the Introduction after results (10)–(20), further

parallel jumps with rates α_j^+ and α_j^- from j_l to $j_{l\pm1}$ can clearly be handled similarly and simply lead to further additive terms in (64) and (10) and (11).

To determine the dispersion, we start from

$$\langle x^2(t)\rangle = \frac{d^2}{N^2}\sum_{l=-\infty}^{+\infty}\sum_{j=0}^{N-1}(j+Nl)^2 P_j(l,t) \tag{65}$$

which leads to

$$\frac{\mathrm{d}}{\mathrm{d}t}\langle x^2(t)\rangle = 2\frac{d^2}{N^2}\left[\sum_{j=0}^{N-1}(u_j - w_j)C_j(t) + \frac{1}{2}\sum_{j=0}^{N-1}(u_j + w_j)b_j(t) + N(\alpha^+ - \alpha^-)C_0(t) + \tfrac{1}{2}N^2(\alpha^+ + \alpha^-)b_0(t)\right], \tag{66}$$

where we have (i) used the master equations (36) and (37), (ii) relying on the rapid convergence of the sums, shifted the summation variables by $j \Rightarrow j \pm 1$ and $l \Rightarrow l \pm 1$ so that, because of the conservation of the probability current, terms proportional to $l^2 P_j(l,t)$ cancel, and (iii) substituted for the sums on l using the definitions (39). Then on using definition (3) of the dispersion, results (61) and (62) for $\langle x(t)\rangle$ and $(\mathrm{d}\langle x(t)\rangle/\mathrm{d}t)$, and recalling the long-time ansatz (43) we find formal expression

$$D_\alpha = \frac{d^2}{N^2}\left[\sum_{j=0}^{N-1}(u_j - w_j)(a_j t + T_j) + \tfrac{1}{2}\sum_{j=0}^{N-1}(u_j + w_j)b_j + N(\alpha^+ - \alpha^-)(a_0 t + T_0) + \tfrac{1}{2}N^2(\alpha^+ + \alpha^-)b_0 - A\sum_{j=0}^{N-1}(a_j t + T_j)\right]. \tag{67}$$

When one uses (51)–(53) the secular terms proportional to t cancel and one is left with

$$D_\alpha = \frac{d^2}{N^2}\left[\sum_{j=0}^{N-1}(u_j - w_j)T_j + \tfrac{1}{2}\sum_{j=0}^{N-1}(u_j + w_j)b_j + N(\alpha^+ - \alpha^-)T_0 + \tfrac{1}{2}N^2(\alpha^+ + \alpha^-)b_0 - A\sum_{j=0}^{N-1}T_j\right]. \tag{68}$$

Now we can substitute for the T_j using expressions (57) and (58). The constant c then cancels [20]. Finally, introducing definition (16) for s_j, enables us to write the dispersion in the forms given in (13)–(20). One sees, as noted above, that the dispersion consists essentially of three terms, the first corresponding to Derrida's original model without jumping, the other two arising directly from the presence of jumps. For symmetric jumping with $\alpha^+ = \alpha^-$, the drift velocity is the same as in the absence of jumps while the dispersion is simply increased by $d^2\alpha^{\pm} r_0/R_N$.

3. Periodic kinetics with branching

Consider the one-dimensional periodic model with branches as presented in Fig. 2. Let the probability of finding the motor at site l at time t in state j of the main sequence (labeled $k=0$) or in state $k=1,\ldots,L$, on the associated branch, be $P_{j,k}(l,t)$. The appropriate master equation for $k=0$ is then

$$\frac{\mathrm{d}}{\mathrm{d}t}P_{j,0}(l,t) = u_{j-1}P_{j-1,0}(l,t) + w_{j+1}P_{j+1,0}(l,t) + \gamma_{j,1}P_{j,1}(l,t) - (u_j + w_j + \beta_{j,0})P_{j,0}(l,t)\,, \tag{69}$$

while for $1 \leqslant k < L$ one has

$$\frac{\mathrm{d}}{\mathrm{d}t}P_{j,k}(l,t) = \beta_{j,k-1}P_{j,k-1}(l,t) + \gamma_{j,k+1}P_{j,k+1}(l,t) - (\beta_{j,k} + \gamma_{j,k})P_{j,k}(l,t)\,, \tag{70}$$

and, finally, for $k=L$,

$$\frac{\mathrm{d}}{\mathrm{d}t}P_{j,L}(l,t) = \beta_{j,L-1}P_{j,L-1}(l,t) - \gamma_{j,L}P_{j,L}(l,t)\,. \tag{71}$$

We may consider the initial condition $P_{j,k}(l;0) = P^0_{j,k}\delta_{l,0}$ and then have the normalization relation

$$\sum_{l=-\infty}^{+\infty}\sum_{j=0}^{N-1}\sum_{k=0}^{L} P_{j,k}(l,t) = 1 \quad (\text{all } t)\,. \tag{72}$$

Following the spirit of Derrida's method as expounded in Section 2, we introduce the auxiliary functions

$$B_{j,k}(t) \equiv \sum_{l=-\infty}^{+\infty} P_{j,k}(l,t), \qquad C_{j,k}(t) \equiv \sum_{l=-\infty}^{+\infty} (j+Nl)P_{j,k}(l,t)\,, \tag{73}$$

for which normalization requires

$$\sum_{j=0}^{N-1}\sum_{k=0}^{L} B_{j,k}(t) = 1 \quad (\text{all } t)\,. \tag{74}$$

The time evolution of the $B_{j,k}(t)$ is given simply by

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}B_{j,0}(t) &= u_{j-1}B_{j-1,0}(t) + w_{j+1}B_{j+1,0}(t) + \gamma_{j,1}B_{j,1}(t) - (u_j + w_j + \beta_{j,0})B_{j,0}(t)\,,\\
\frac{\mathrm{d}}{\mathrm{d}t}B_{j,1}(t) &= \beta_{j,0}B_{j,0}(t) + \gamma_{j,2}B_{j,2}(t) - (\beta_{j,1} + \gamma_{j,1})B_{j,1}(t)\,,\\
&\vdots\\
\frac{\mathrm{d}}{\mathrm{d}t}B_{j,L}(t) &= \beta_{j,L-1}B_{j,L-1}(t) - \gamma_{j,L}B_{j,L}(t)\,,
\end{aligned} \tag{75}$$

while the $C_{j,k}(t)$ must satisfy

$$\frac{\mathrm{d}}{\mathrm{d}t}C_{j,0}(t) = u_{j-1}C_{j-1,0}(t) + w_{j+1}C_{j+1,0}(t) + \gamma_{j,1}C_{j,1}(t) - (u_j + w_j + \beta_{j,0})C_{j,0}(t) + u_{j-1}B_{j-1,0}(t) - w_{j+1}B_{j+1,0}(t)\,,$$

$$\frac{\mathrm{d}}{\mathrm{d}t}C_{j,1}(t) = \beta_{j,0}C_{j,0}(t) + \gamma_{j,2}C_{j,2}(t) - (\beta_{j,1} + \gamma_{j,1})C_{j,1}(t)\,,$$

$$\vdots$$

$$\frac{\mathrm{d}}{\mathrm{d}t}C_{j,L}(t) = \beta_{j,L-1}C_{j,L-1}(t) - \gamma_{j,L}C_{j,L}(t)\,. \tag{76}$$

Arguing, as before, that the long-time behavior of $P_{j,k}(l,t)$ must represent a probability packet drifting steadily, we introduce the ansatz

$$B_{j,k}(t) \to b_{j,k}, \quad C_{j,k}(t) - a_{j,k}t \to T_{j,k} \tag{77}$$

for $t \to \infty$. By (75) and (76) the coefficients $b_{j,k}$ must then satisfy

$$w_{j+1}b_{j+1,0} - u_j b_{j,0} = w_j b_{j,0} - u_{j-1}b_{j-1,0} + (\beta_{j,0}b_{j,0} - \gamma_{j,1}b_{j,1})\,, \tag{78}$$

$$\beta_{j,0}b_{j,0} - \gamma_{j,1}b_{j,1} = \beta_{j,1}b_{j,1} - \gamma_{j,2}b_{j,2} = \cdots = \beta_{j,L-1}b_{j,L-1} - \gamma_{j,L}b_{j,L} = 0\,, \tag{79}$$

while the $a_{j,k}$ and $T_{j,k}$, should be determined from

$$a_{j,0} = u_{j-1}T_{j-1,0} + w_{j+1}T_{j+1,0} - (u_j + w_j)T_{j,0} + u_{j-1}b_{j-1,0} - w_{j+1}b_{j+1,0}$$
$$-(\beta_{j,0}T_{j,0} - \gamma_{j,1}T_{j,1})\,, \tag{80}$$

$$a_{j,1} = (\beta_{j,0}T_{j,0} - \gamma_{j,1}T_{j,1}) - (\beta_{j,1}T_{j,1} - \gamma_{j,2}T_{j,2}), \quad \ldots,$$

$$a_{j,L} = \beta_{j,L-1}T_{j,L-1} - \gamma_{j,L}T_{j,L}\,, \tag{81}$$

and from the set

$$w_{j+1}a_{j+1,0} - u_j a_{j,0} = w_j a_{j,0} - u_{j-1}a_{j-1,0} + (\beta_{j,0}a_{j,0} - \gamma_{j,1}a_{j,1})\,, \tag{82}$$

$$\beta_{j,0}a_{j,0} - \gamma_{j,1}a_{j,1} = \beta_{j,1}a_{j,1} - \gamma_{j,2}a_{j,2} = \cdots = \beta_{j,L-1}a_{j,L-1} - \gamma_{j,L}a_{j,L} = 0\,, \tag{83}$$

which precisely matches (78) and (79).

The side-branch relations (79) are readily solved recursively: recalling the notation (5), one finds

$$b_{j,k} = \Pi_j^{\beta,k} b_{j,0} \quad (k = 1,\ldots,L) \tag{84}$$

and sees that the β and γ terms drop out of (78) which then reduces to the same form as (45) in Section 2. Consequently, the method of solution used to derive (47) works, the only change arising from the normalization of the $b_{j,k}$ which now follows from (74). Thus we obtain

$$b_{j,0} = r_j / R_N^{\beta}\,, \tag{85}$$

where the r_j were already defined in (12) while R_N^{β} is given by (22). As noted, the recursion relations (82) and (83) for the $a_{j,k}$ have the same form as for the $b_{j,k}$ and so, as in Section 2, we are led to

$$a_{j,k} = A b_{j,k} \quad \text{with} \quad A = N(1 - \Pi_1^N)/R_N^{\beta}\,. \tag{86}$$

The remainder of the analysis now proceeds on the basis of (80) and (81) in completely parallel fashion to that presented in Section 2 for the model with jumps. The

results for the drift velocity V_β and the dispersion D_β are given in (21)–(28) of the Introduction. Inspection of the analysis leading from (73) to (85) reveals that the only changes introduced by adding further branches, trees, etc., arise from the overall normalization requirement which led here to the replacement of r_j by r_j^β and R_N by R_N^β: see (85) and (22).

4. Periodic kinetics with death

Finally, we consider the periodic sequential model with the possibility of detachment from each state with rates $\delta_j \equiv \delta_{j\pm N} \geqslant 0$ as depicted in Fig. 3. The time evolution of the probability $P_j(l,t)$ of finding a live motor in state j at site l at time t is now governed by the master equation

$$\frac{\mathrm{d}}{\mathrm{d}t}P_j(l,t) = u_{j-1}P_{j-1}(l,t) + w_{j+1}P_{j+1}(l,t) - (u_j + w_j + \delta_j)P_j(l,t)\,, \tag{87}$$

where, as previously, we may accept a localized initial condition of the form

$$P_j(l;0) = P_j^0\delta_{l,0} \quad \text{with} \quad \sum_{j=0}^{N-1} P_j^0 = 1\,. \tag{88}$$

However, because of the death processes, the overall normalization of $P_j(l,t)$, as previously stated in (38), is no longer valid. Likewise, the conservation of the probability current, which also played a crucial role in the previous analysis, is not now available.

Nevertheless, heuristic considerations suggest that the long-time behavior should again describe a steadily drifting and diffusively broadening packet of probability with, *however*, an overall amplitude that decays exponentially in time. Accordingly, we ask whether one might find long-time solutions of the master equation (87) of the form

$$P_j(l,t) \approx \mathrm{e}^{-\lambda t - \tau_j}\tilde{P}_j(l,t)\,, \tag{89}$$

where the decrement λ and the periodic state coefficients, $\tau_j \equiv \tau_{j\pm N}$, are to be fixed so that $\tilde{P}_j(l,t)$ satisfies the "renormalized", *probability conserving* master equation

$$\frac{\mathrm{d}}{\mathrm{d}t}\tilde{P}_j(l,t) = \tilde{u}_{j-1}\tilde{P}_{j-1}(l,t) + \tilde{w}_{j+1}\tilde{P}_{j+1}(l,t) - (\tilde{u}_j + \tilde{w}_j)\tilde{P}_j(l,t) \tag{90}$$

with suitable "renormalized" periodic rates $\tilde{u}_j = \tilde{u}_{j\pm N}$ and $\tilde{w}_j = \tilde{w}_{j\pm N}$. Clearly, if such solutions can be found, we will require only those for which the real part of λ is smallest since these must be the longest lived. (In actuality we expect, in general, to find a unique, real, positive λ of smallest magnitude.)

Now if, as is in reality implied by (88), a localized initial condition of the form $\tilde{P}_j(l;0) = \tilde{P}_j^0\delta_{l,0}$ is acceptable, the renormalized problem is of precisely the form originally treated by Derrida (see Ref. [20] and Section 2, above). Thus, in the presence of deaths the velocity and dispersion, V_δ and D_δ, of the *surviving* motor proteins, i.e., discounting the overall exponential decay of probability, may be obtained simply by replacing u_j and w_j in Derrida's results by $\tilde{u}_j$ and $\tilde{w}_j$, so yielding the expressions reported in the Introduction: see (29) and (30).

To proceed, let us substitute the ansatz (89) in the master equation (87) and multiply by $e^{\lambda t+\tau_j}$ to obtain

$$\frac{d}{dt}\tilde{P}_j(l,t) = u_{j-1}e^{\tau_j-\tau_{j-1}}\tilde{P}_{j-1} + w_{j+1}e^{\tau_j-\tau_{j+1}}\tilde{P}_{j+1} - (u_j + w_j + \delta_j - \lambda)\tilde{P}_j \,. \quad (91)$$

Matching the first two terms here to those in (90) yields the relations

$$\tilde{u}_j = u_j\varphi_{j+1}/\varphi_j \quad \text{and} \quad \tilde{w}_j = w_j\varphi_{j-1}/\varphi_j \quad \text{with} \quad \varphi_j = e^{\tau_j} \,; \quad (92)$$

these should be compared with (6) in the Introduction. However, matching the last terms in (91) and (90) yields a condition on $(\tilde{u}_j + \tilde{w}_j)$. On multiplication by φ_j, this may be rewritten as

$$-w_j\varphi_{j-1} + (u_j + w_j + \delta_j)\varphi_j - u_j\varphi_{j+1} = \lambda\varphi_j \quad (93)$$

for $j = 0, 1, \ldots, N-1$ with, clearly, the periodicity conditions $\varphi_{-1} = \varphi_{N-1}$ and $\varphi_N = \varphi_0$ understood.

Evidently, this condition can be read as the eigenvalue equation $\mathbf{M}\boldsymbol{\varphi} = \lambda\boldsymbol{\varphi}$, where $\mathbf{M}$ is the $N \times N$ matrix specified in (8) and (9) of the Introduction while $\boldsymbol{\varphi}$ is the column vector $[\varphi_j]$ which may be normalized by $\varphi_0 = 1$, in accord with (7). Thus $\lambda = \lambda_0$ is to be chosen as the smallest eigenvalue of $\mathbf{M}$ and the required φ_j are the components of the corresponding eigenvector.

For finite N we expect in general that, as mentioned, λ_0 will be real, positive and nondegenerate: should λ_0 prove degenerate or should a complex pair of eigenvalues have the smallest real part, etc., further investigation of the asymptotic behavior of $P_j(l,t)$ would be required. If we neglect such possibilities, however, we have now established the results claimed in the Introduction for periodic sequential processes with deaths.

The specific expressions for $N = 2$ quoted in (31)–(35) follow readily by solving the quadratic equation $|\mathbf{M} - \lambda\mathbf{I}| = 0$ and selecting the appropriate root. As can then be seen from (35), the positivity of either u_0u_1 *or* w_0w_1 is sufficient to ensure that λ_0 is real and nondegenerate. More generally note, by virtue of (93) with (7), that one may express the decrement as

$$\lambda = \delta_0 + u_0(1 - \varphi_1) + w_0(1 - \varphi_{N-1}) \,. \quad (94)$$

In the trivial case where all the death rates are the same, i.e., $\delta_j = \delta$, one readily checks from (93), etc., that $\lambda = \delta$ and $\varphi_j = 1$ (all j), as is to be anticipated.

5. Applications to motor protein models

To illustrate the application of our various results for the extended periodic sequential kinetic schemes, we recall one of the $N = 2$ sequences, namely model (d), that was discussed in Refs. [10,11] in the context of experiments on kinesin [15–17]. This motor protein moves processively (i.e., with small death rates) along microtubules taking steps of size $d = 8.2$ nm [1,2,15,16]. It must be emphasized, however, that model (d) was

Table 1
Values of $N = 2$ model motor protein parameters illustrating the effects of including jumping, branching (with $L_0 = 0$ and $L_1 = 1$), and death processes. The theory of Refs. [10,11] is invoked for force calculations

	Model	Zero-load properties			Stall force
	$u_j^0, w_j^0, \theta_j^{\pm}, \theta_\alpha^{\pm}$: see (96)–(100)	$\ln \Gamma \equiv \varepsilon$	V^0 (nm/s)	D^0 (nm^2/s]	F_S (pN)
(i)	(d)	11.1	763	1774	5.55
(ii)	With jumps				
	$\alpha^+ = \alpha^- = 20\ \mathrm{s}^{-1}$	11.1	763	2400	2.31
(iii)	With a branch				
	$\beta_{1,0} = \gamma_{1,1} = 200\ \mathrm{s}^{-1}$	11.1	497	1720	5.55
	With death				
(iv)	$\delta_0 = 200\ \mathrm{s}^{-1},\ \delta_1 = 0$	11.1	711	1819	5.55
(v)	$\delta_0 = 0,\ \delta_1 = 200\ \mathrm{s}^{-1}$	11.1	674	1830	5.55

not specifically designed to provide a description of kinesin — work in that direction is proceeding in the light of the more extensive experiments by Visscher et al. [19]. However, the magnitudes of the selected rates for model (d), and, in particular, the value of the basic product [10,11]

$$\Gamma = 1/\Pi_1^N = \prod_{j=0}^{N-1} \frac{u_j}{w_j} \equiv e^{\varepsilon} \tag{95}$$

were chosen to accord roughly with experimental data (inasfar as available [10]).

Explicitly, model (d) can be specified by rates

$$u_0^0 = u_1^0 = 200\ \mathrm{s}^{-1}, \quad w_0^0 = 30\ \mathrm{s}^{-1}, \quad w_1^0 = 0.02\ \mathrm{s}^{-1}\,. \tag{96}$$

These rates lead to $\varepsilon = 11.1$ in (95), which value correlates sensibly with the reduced free energy, $\Delta G_0/k_BT$, released by the hydrolysis of one ATP molecule at ambient temperatures, say $T = 300$ K [10,11]. Note that the superscript zero on the rates here indicates the operation of the motor under *zero load* force F. The corresponding velocity and dispersion, $V^0 = V(F = 0)$ and $D^0 = D(F = 0)$ are presented in Table 1 line (i). Note that the values are not unreasonable [10].

Also shown in Table 1 are particular rate parameters (α, β, γ and δ), selected to illustrate the effects of extending model (d) to include (ii) jumps in the symmetric ("thermal diffusion") situation, $\alpha^+ = \alpha^-$; (iii) a single branch of length $L_1 = 1$ emanating from state $j = 1$; and (iv) death (or detachment) only from the resting state $j = 0$ or (v) only "in process," i.e., from state $j = 1$. One sees, first, in line (ii) of the table, that the inclusion of symmetric jumps has no effect on the zero-load velocity, V^0, although, naturally, the dispersion increases markedly. When the motor spends time undergoing branching, the velocity is decreased and, although less strongly, the dispersion under zero load also falls: see line (iii). Conversely, the same death rate from states $j = 0$ or 1, reduces the zero-load velocity by differing amounts and increases, in these cases, the zero-load dispersion, D^0: see lines (iv) and (v).

Now, as mentioned in the Introduction, to determine the force exerted by a motor described by a kinetic model, further theory is evidently necessary. The same is true if one is to allow for the action of loads on the motor: clearly these must modify the transition rates in some fashion. An appropriate general formulation has been developed by the authors [10,11]: we appeal to that for the results presented here without further exposition beyond indicating that, under a load F, the forward and backward rates, u_j and w_j, should be modified by factors

$$\exp(-\theta_j^+ Fd/k_BT) \quad \text{and} \quad \exp(+\theta_j^- Fd/k_BT)\,, \tag{97}$$

respectively, where $\theta = \sum_{j=0}^{N-1}(\theta_j^+ + \theta_j^-)$ may reasonably be taken as unity. The crucial feature of these expressions is the presence of the "load distribution factors," θ_j^+ and θ_j^-; these serve to describe how the overall load force, F, acts on the various transitions between the internal motor states, j. As such they represent an intrinsic (and inescapable!) part of the mechanochemical description of a molecular motor. For simplicity, the values adopted for model (d) were

$$\theta_0^+ = \theta_1^+ = 0 \quad \text{and} \quad \theta_0^- = \theta_1^- = \tfrac{1}{2}\,. \tag{98}$$

When jumps along the track are also present, it is clear physically that the corresponding forward and backwards rates should also be modified by the action of a load, F. Specifically, then, we suppose

$$\alpha^+ \Rightarrow \alpha_{(F)}^+ = \alpha^+ \mathrm{e}^{-\theta_\alpha^+ Fd/k_BT}, \quad \alpha^+ \Rightarrow \alpha_{(F)}^- = \alpha^- \mathrm{e}^{+\theta_\alpha^- Fd/k_BT}\,, \tag{99}$$

where $\theta_\alpha^+ + \theta_\alpha^- = \theta_\alpha$ (which we will again take as unity). For the purposes of numerical illustration on the basis of model (d), we will accept the simple assignment

$$\theta_\alpha^+ = \theta_\alpha^- = \tfrac{1}{2}\,. \tag{100}$$

In principle, the branching and death rates could also be sensitive to load. Indeed, it is observed, in particular, that the rate of detachment of kinesin from a microtubule increases under high loads (at fixed [ATP]) [19]. In an optimal model, therefore, one or more of the death rates should probably increase with F. However, we assume here that only the principal sequential rates, $u_j^{(F)}$ and $w_j^{(F)}$, vary with F [in accord with (97) and (98)]. Likewise, we will suppose that the branching rates $\beta_{1,0}$ and $\gamma_{1,1}$ remain independent of load.

The behavior of the velocity, $V(F)$, and dispersion, $D(F)$, as the load varies can now be calculated from the results derived above. When F increases to the stalling load, F_S, the velocity approaches zero; i.e., the motor "stalls." Results (21) and (29) for the velocities combined with (6) and definition (95), show that V vanishes when $\Gamma = 1$. Via (97), this leads to the expression

$$F_S = \varepsilon k_BT/d \tag{101}$$

for the stalling load in the models with branching and death. This conclusion is identical to the result originally found for the simple sequential models [10,11]. In these cases, therefore, the stalling force for model (d) remains fixed at 5.55 pN (see Table 1) even when branching and deaths are included.

When jumping is present, however, one must take account of (99) which destroys any zero-load symmetry. Then the velocity $V(F)$ is given by (10) and (11) with (98) and (99). Since not only α^+ and α^- but also r_0 [in (11) and (12)] depend on the reduced load, $\check{F} \equiv F_S d/k_B T$, one is led to a transcendental equation for the reduced stalling force, $\check{F}_S$, which is generally intractable. If α^+ and α^- are sufficiently small, however, one can use

$$\check{F} \equiv F_S d/k_B T \approx \varepsilon - r_0(\check{F} = \varepsilon)(\alpha^+ e^{-\theta_\alpha^+ \varepsilon} - \alpha^- e^{+\theta_\alpha^- \varepsilon}) . \tag{102}$$

For model (d) with (100) and the chosen $\alpha^+ = \alpha^-$, line (ii) of Table 1 shows the numerically computed change in stalling force induced by the jumping: it is negative and quite large in this case.

We may mention in passing that a general "barometric" measure, f_B, of the force exerted by a kinetic motor model under, in essence, zero-load conditions was introduced in Refs. [10,11]. For the simple sequential models this led to the same value as in (101) (subject to the condition $\theta = 1$). This remains true for the extended models with branching and deaths; but with jumps present a different result is again found, namely,

$$f_B = (k_B T/d) \ln[(1 + \alpha^+ r_0/(e^{-\varepsilon} + \alpha^- r_0)] \tag{103}$$

which furthermore, no longer agrees with F_S (as is not really surprising).

Now for the original model (d) a reduced velocity-load plot, i.e., $V(F)/V(0)$ vs. $\eta \equiv F/F_S$, has already been presented [10,11]: one finds that $V(F)$ decreases monotonically as F increases, which is a typical situation although exceptions are possible [11]. We focus here, however, on the dispersion or effective diffusion constant, D, which gives additional insight into the operation of a molecular motor [4,15,19]. Specifically, the "randomness" $r(F) = 2D/dV$ represents an interesting dimensionless measure [15,19] since it is subject, in the simple kinetic models, to the lower bound $r \geqslant 1/N$ [10,11].

In Fig. 4 we thus display the variation of the randomness with reduced load for the unadorned model (d) [solid curves labeled (i)] and for the model supplemented, as in Table 1, (ii) by jumps; (iii) by a side-branch process; and (iv) and (v) by death (or detachment). It is interesting that even for the pure model (d) the variation of r with F reveals significant structure: and these features are reflected in the recent observations [19].

As already noted, one sees from Fig. 4(a) that the inclusion of jumping and branching increases the dispersion at low loads and this remains true up to moderate loads for the selected parameters. The *relative* effects of the side branch on the randomness decreases, however, quite sharply at higher loads. The effects of including death processes is more subtle: in the first case, (iv) where motor detachment occurs only from the "unactivated" or "resting state" $j = 0$, the randomness always increases. On the other hand, when detachment occurs only "in process", i.e., from state $j = 1$, the randomness (of the surviving motors) at intermediate loads is actually somewhat *reduced*: see plot (v). This effect arises primarily because the relative velocity becomes larger at intermediate loads.

Clearly, these examples are no more than indicative of the usefulness of the extensions to the original periodic sequential kinetic models we have studied here. But they serve to suggest how detailed observations of real molecular motors under load (and, also, under varying power source [19]) may cast light on the mechanisms. Further applications should, certainly, be tied to observations of real systems as far as practicable. Nevertheless, on the theoretical side we plan to extend the analysis to the more general class of models in which waiting-time distributions, $\psi_j^{\pm}(t)$, etc., replace the simple kinetic schemes discussed here (which correspond to $\psi_j^{\pm}(t) \propto \mathrm{e}^{-\lambda_j^{\pm} t}$). The initial steps in that direction have already been sketched [10,11].

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