Stochastic model of intraflagellar transport

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We present a stochastic model of filament growth driven by the motor-assisted transport of particles along the filament. We show how the growth can be analyzed in terms of a sequence of first passage times for a particle hopping between the two ends of the filament, and use this to calculate the mean and variance of the length as a function of time. We determine how the growth depends on the waiting time density of the underlying hopping process, and highlight differences in the growth generated by normal and anomalous transport, for which the mean waiting time is finite and infinite, respectively. In the case of normal transport, we determine the length at which there is a balance between particle-driven assembly and particle-independent disassembly of the filament. The existence of such a balance point is thought to provide a mechanism for flagellar length control.

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I. INTRODUCTION

A major unanswered question in cell biology is how cells regulate the size of their organelles [1]. Size control mechanisms, which are critical for proper cell function, can be distinguished according to whether the underlying structure is static or dynamic. Static structures are those that remain intact once assembled, only undergoing further assembly and disassembly if they are regenerating in response to damage. One suggested mechanism for static size control involves a molecular ruler, in which the organelle size is fixed by the physical extent of an individual molecule. This occurs for example in the case of bacteriophage tails [2]. A second type of static mechanism is sensor-based size control, in which a signal transduction pathway monitors organelle size and modulates assembly accordingly. An interesting example of this has recently been suggested in a model of length control for *salmonella* flagellar motor filaments [3]. In this model, a length-dependent diffusive flux of secretory molecules is transduced into a chemical signal by means of a negative feedback circuit involving the secretant. Dynamic structures, on the other hand, are constantly turning over so that in order for them to maintain a fixed size, there must be a balance between the rates of assembly and disassembly. If these rates depend on the size in an appropriate way then there will be a unique balance point that stabilizes the size of the organelle. Recent experimental work suggests that such a dynamic mechanism may occur in eukaryotic flagella [4,5]. These are microtubule-based structures that extend to about 10 μm from the cell and are surrounded by an extension of the plasma membrane. They are at least an order of magnitude longer than bacterial flagella.

Flagellar length control is a particularly convenient system for studying organelle size regulation, since a flagellum can be treated as a one-dimensional structure whose size is characterized by a single length variable. The length of a eukaryotic flagellum is important for proper cell motility, and a number of human diseases appear to be correlated with abnormal length flagella [6]. Radioactive pulse labeling has been used to measure protein turnover in the flagella of *Chlamydomonas*, a unicellular green alga with genetics similar to budding yeast [4]. Such measurements have suggested that turnover of tubulin occurs at the distal+end of flagellar microtubules, and that the assembly part of the turnover is mediated by intraflagellar transport (IFT). This is a motor-assisted motility within flagella in which large protein complexes move from one end of the flagellum to the other [7,8]. Particles of various size travel to the flagellar tip (anterograde transport) at 2.0 μm/s, and smaller particles return from the tip (retrograde transport) at 3.5 μm/s after dropping off their cargo of assembly proteins at the + end. A schematic diagram of IFT transport is shown in Fig. 1. Immunoflourescence analysis indicates that the number of IFT particles (estimated to be in the range of 1–10) is independent of length [4,5]. If a fixed number of transport complexes M move at a fixed mean speed $\bar{v}$, then the rate of transport and assembly should decrease inversely with the flagellar length L. On the other hand, measurements of the rate of flagellar shrinkage when IFT is blocked indicate that the rate of disassembly is length independent. This has motivated the following simple deterministic model for length control [4]

$$\frac{dL}{dt} = \frac{a\bar{v}M}{2L} - V, \tag{1}$$

where a is the effective size of the precursor protein transported by each IFT particle and V is the speed of disassembly. Clearly, Eq. (1) has a unique stable equilibrium given by

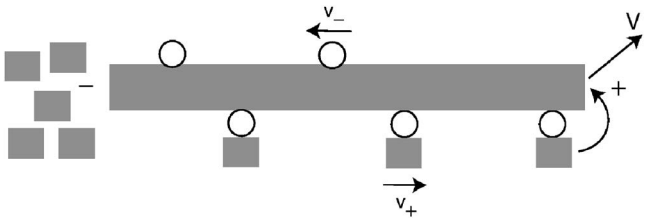

FIG. 1. Schematic diagram of IFT, in which IFT particles travel with speed $v_{\pm}$ to the $\pm$ end of a flagellum. When an IFT particle reaches the + end it releases its cargo of protein precursors that contribute to the assembly of the flagellum. Disassembly occurs independently of IFT transport at a speed V.

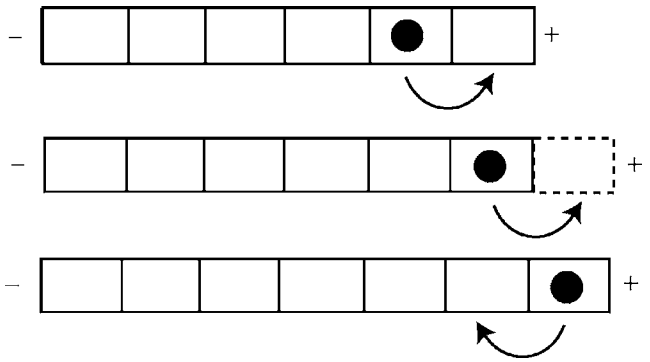

FIG. 2. Particle hopping along a one-dimensional filament that is modeled as a discrete lattice. When the particle reaches the + end of the filament, a lattice site is added to form the new + end and the particle reverses its direction. The particle also reverses direction at the − end.

$L^*=a\bar{v}M/2V$. Using the experimentally based values $M=10$, $\bar{v}=2.5$ μm/s, $L^*=10$ μm, and $V=0.01$ μm/s, the effective precursor protein size is estimated to be $a\approx 10$ nm. In the case of a single IFT particle ($M=1$), the same equilibrium length would be obtained for a disassembly speed of $V=0.001$ μm/s. Alternatively, a single particle could unload M precursor proteins whenever it reaches the distal end of the filament.

At the microscopic level the motion of molecular motors is stochastic rather than deterministic. Therefore, it is interesting to investigate the dynamics of filament growth driven by stochastic particle transport. In this paper we consider a very simple stochastic model in which a single particle hops unidirectionally along a single filament track, reversing direction whenever it hits the ± ends of the filament. In addition, whenever the particle reaches the + end, the length of the filament is increased by a fixed amount. Thus the growth of the filament can be described in terms of a sequence of first passage times for a particle hopping between the two ends of the filament. In the case of pure growth (no disassembly) we calculate the mean and variance of the filament length as a function of time, and show how these quantities depend on the waiting time density of the hopping process. In particular, we highlight the differences in growth generated by normal transport (finite mean waiting time) and by anomalous transport (infinite mean waiting time). In the case of normal transport, we determine the expected length at which there is a balance between particle-driven assembly and particle-independent disassembly.

II. PARTICLE HOPPING MODEL

Consider a particle hopping along a single filament track as shown in Fig. 2. The track is modeled as a discrete one-dimensional lattice with lattice spacing ℓ. Suppose that there are initially N_0+1 lattice sites labeled $n=0,\ldots,N_0$, with $n=0$ corresponding to the − end and $n=N_0$ to the + end. The initial length of the filament is thus $L_0=N_0\ell$. Starting at the − end at time $t=0$, the particle steps towards the + end. The times τ between successive steps are taken to be independent, identically distributed random variables with a common waiting time density $\psi^+(\tau)$. When the particle reaches the current + end, the length of the filament is increased by one lattice site to form the new + end. Once the particle has reached this new lattice site, the hopping process reverses direction with a corresponding waiting time density $\psi^-(t)$. Two distinct waiting time densities are introduced in order to allow for an asymmetry in the anterograde and retrograde motions. After returning to the − end the particle reverses direction again and the process continues iteratively. For simplicity, we ignore additional delays associated with the particle reversing direction at either end.

Denoting the successive times at which the particle returns to the ± end by $T_j^{\pm}, j\geqslant 1$, there is the following sequence of events: the particle travels a distance $L_0+j\ell$ from − to + over the time interval $[T_{j-1}^-,T_j^+]$ and then a distance $L_0+j\ell$ from + to − over the time interval $[T_j^+,T_j^-]$ for $j\geqslant 1$ with $T_0^-=0$. Each time the particle makes a return trip to the + end, the length of the filament is increased by ℓ. Let $f_j^{\pm}(t)dt$ be the probability that $t<\Delta T_j^{\pm}<t+dt$ with $\Delta T_j^+=T_j^+-T_{j-1}^-$ and $\Delta T_j^-=T_j^--T_j^+$. Then $f_j^+(t)$ is the first passage time density for a particle to travel a distance $L_0+j\ell$ starting from the − end (anterograde portion of jth roundtrip), and $f_j^-(t)$ is the first passage time density for a particle to travel a distance $L_0+j\ell$ from the + end (retrograde portion of jth roundtrip). Let $L(t)$ be the length of the flagellum at time t and introduce the length probability $P_j(t)=\mathrm{Prob}[L(t)=L_j]$, where $L_j=L_0+j\ell$. It follows that $L(t)=L_j$ if and only if $T_j^+\leqslant t<T_{j+1}^+$. Hence,

$$P_j(t)=\int_0^t F_{j+1}(t-t')g_j(t')dt', \tag{2}$$

where $g_j(t')$ is the probability density that the particle has just made the jth visit to the + end at time t' and $F_{j+1}(t-t')$ is the probability that the particle has not made the $(j+1)$th visit during the time interval $t-t'$. In terms of the first passage time densities

$$F_j(t)=\int_t^{\infty}\left[\int_0^{t'} f_j^+(t'-t'')f_{j-1}^-(t'')dt''\right]dt' \tag{3}$$

and

$$g_j(t)=\int_0^t\int_0^{t'} f_j^+(t-t')f_{j-1}^-(t'-t'')g_{j-1}(t'')dt''dt' \tag{4}$$

for $j\geqslant 2$ with $g_1(t)=f_1^+(t)$. We solve the iterative equation for $g_j(t)$ using Laplace transforms and substitute the result into the Laplace transform of Eq. (2). Since $\hat{F}_j(s)=[1-\hat{f}_j^+(s)\hat{f}_{j-1}^-(s)]/s$, it follows that

$$\hat{P}_j(s)=\frac{\hat{g}_j(s)-\hat{g}_{j+1}(s)}{s}, \tag{5}$$

with

$$\hat{g}_j(s) = \hat{f}_j^+(s)\prod_{k=1}^{j-1}[\hat{f}_k^+(s)\hat{f}_k^-(s)]. \quad (6)$$

Note that $\Sigma_{j=0}^{\infty}\hat{P}_j(s)=s^{-1}$, which reflects the normalization condition $\Sigma_{j=0}^{\infty}P_j(t)=1$.

It remains to determine $\hat{f}_j^{\pm}(s)$ and, hence, $\hat{g}_j(s)$ in terms of the waiting time densities $\psi^{\pm}(t)$. Suppose that the particle has just reached the $\mp$ end at time $t=0$. Let $\psi_n^{\pm}(t)$ be the probability density for making the nth step towards the $\pm$ end at time t. This satisfies the iterative equation

$$\psi_n^{\pm}(t) = \int_0^t \psi^{\pm}(\tau)\psi_{n-1}^{\pm}(t-\tau)d\tau, \quad (7)$$

with $\psi_1^{\pm}(\tau)=\psi^{\pm}(\tau)$. Laplace transforming this equation gives

$$\hat{\psi}_n^{\pm}(s) = \{\hat{\psi}^{\pm}(s)\}^n. \quad (8)$$

It follows that the Laplace transforms of the first passage time densities are

$$\hat{f}_k^{\pm}(s) = \{\hat{\psi}^{\pm}(s)\}^{N_0+k}. \quad (9)$$

Substituting into Eq. (6) and evaluating the product over k yields the result

$$\hat{g}_j(s) = \{\hat{\psi}^+(s)\}^{jN_0+j(j+1)/2}\{\hat{\psi}^-(s)\}^{jN_0+j(j-1)/2}. \quad (10)$$

We have restricted our analysis to the case of unidirectional transport, since we are interested in the particular problem of intraflagellar transport (see Sec. IV). Note, however, that it is straightforward to generalize our analysis to allow for bidirectional transport, in which the particle undergoes a (biased) random walk around the filament. The delivery of cargo to the + end is now formulated in terms of a first passage time problem on a ring. It is still necessary to keep track of the times the particle returns to the − end, since a particle returning to the + end cannot deliver any cargo proteins unless it has first "refilled" at the − end.

III. MEAN AND VARIANCE OF FILAMENT LENGTH

A useful way to characterize the stochastic growth of the filament is in terms of the mean and variance of the length $L(t)$. Let $\eta_n(t)=\Sigma_{j=0}^{\infty}j^nP_j(t)$ denote the nth moment of the distribution $P_j(t)$. Then

$$\langle L\rangle = L_0 + \ell\,\eta_1(t), \quad \langle \Delta L^2\rangle = \ell^2[\eta_2(t)-\eta_1(t)^2]. \quad (11)$$

We will determine the large-t behavior of the mean and variance in terms of the small-s behavior of the Laplace transforms $\hat{\eta}_n(s)$. First, note from Eq. (5) that

$$\hat{\eta}_1(s) = \frac{1}{s}\sum_{j=1}^{\infty}\hat{g}_j(s), \quad \hat{\eta}_2(s) = \frac{1}{s}\sum_{j=1}^{\infty}(2j-1)\hat{g}_j(s). \quad (12)$$

For the sake of simplicity, we evaluate these sums in the symmetric case $\psi^+=\psi^-=\psi$, and set $L_0=0$, since the leading order large-t behavior will be independent of L_0. Then $\hat{g}_j(s)=e^{-j^2\gamma(s)}$ with

$$\gamma(s) = -\ln\hat{\psi}(s). \quad (13)$$

From the definition of the Laplace transform

$$\hat{\psi}(s) = \int_0^{\infty} e^{-st}\psi(t)dt = \int_0^{\infty}\{1-st+s^2t^2/2-\cdots\}\psi(t)dt, \quad (14)$$

so that in the small-s limit

$$\hat{\psi}(s) = 1 - \tau s + \hat{\psi}_2 s^2/2\cdots, \quad (15)$$

provided that mean (and variance) of the waiting time between steps is finite, that is, $\tau=\int_0^{\infty}t\psi(t)dt<\infty$ and $\hat{\psi}_2=\int_0^{\infty}t^2\psi(t)dt<\infty$. We will refer to this case as normal particle transport along the filament. We will also consider a form of anomalous transport, in which the mean waiting time is infinite and the Laplace transform of the waiting time density has noninteger power-law behavior in the small-s expansion [9]

$$\hat{\psi}(s) = 1 - Bs^{\beta} + \cdots, \quad 0<\beta<1. \quad (16)$$

In the limit $s\to 0$, the function $\gamma(s)$ has the asymptotic expansion $\gamma(s)\sim\tau s$ for normal transport and $\gamma(s)\sim Bs^{\beta}$ for anomalous transport.

In order to evaluate the sums in Eq. (12), we use the Poisson summation formula to derive the identity (after rescaling)

$$\delta_{n,0} + 2\sum_{j=1}^{\infty}j^n e^{-j^2\gamma(s)} = \left[\frac{1}{\gamma(s)}\right]^{(n+1)/2} \times\left\{c_n(0) + 2\sum_{p=1}^{\infty}c_n[p/\sqrt{\gamma(s)}]\right\} \quad (17)$$

with

$$c_n(z) = \int_{-\infty}^{\infty}|y|^n\cos(2\pi zy)e^{-y^2}dy.$$

In the limit $s\to 0$, $z=p/\sqrt{\gamma(s)}\to\infty$ for $p\neq 0$ and the oscillatory integral $c_n(z)$ can be evaluated by performing the change of variables $\xi=y/z$ and using steepest descents. This shows that $c_n(z)\sim z^n e^{-\pi^2z^2}$ in the limit $z\to\infty$, which is exponentially small compared to $c_n(0)$. Therefore, in the small-s limit, we keep only the term $c_n(0)$ in Eq. (17) and use the asymptotic expansion of $\gamma(s)$. Let us first consider the case of normal transport with $\gamma(s)\sim\tau s$. Evaluating Eq. (17) in the limit $s\to 0$ for $n=0,1$ and substituting into Eq. (12) shows that

$$\hat{\eta}_1(s) \sim \frac{1}{2s}\sqrt{\frac{\pi}{\tau s}}, \quad \hat{\eta}_2(s) \sim \frac{1}{\tau s^2}. \quad (18)$$

Using a Tauberian theorem [9], we can then invert the Laplace transforms to obtain

$$\eta_1(t) \sim \sqrt{t/\tau}, \quad \eta_2(t) \sim t/\tau. \tag{19}$$

It follows from Eq. (11) that $\langle L\rangle \sim \ell\sqrt{t/\tau}$ and $\langle \Delta L^2\rangle \sim 0$. Differentiating $\langle L\rangle$ with respect to t, we find that in the large-t limit, the mean length evolves according to Eq. (1) with $V=0$ (no disassembly), $Ma=\ell$ and $\bar{v}=\ell/\tau$. The mean velocity $\bar{v}$ of the particle is simply equal to the length ℓ of a single step along the filament divided by the mean waiting time τ. If the variance of the waiting times is also finite then one can expand $\gamma(s)$ to second order in s and show that $\langle \Delta L^2\rangle = \mathcal{O}(1)$ with $\sqrt{\langle \Delta L^2\rangle}/\langle L\rangle \sim t^{-1/2}$ as $t\to\infty$.

The above analysis can be repeated for anomalous transport using the asymptotic expansion $\gamma(s)\sim Bs^{\beta}$ for $0<\beta<1$. In this case

$$\hat{\eta}_1(s) \sim \frac{1}{2s}\sqrt{\frac{\pi}{Bs^{\beta}}}, \quad \hat{\eta}_2(s) \sim \frac{1}{Bs^{1+\beta}}. \tag{20}$$

Applying a Tauberian theorem [9] gives

$$\eta_1(t) \sim \frac{t^{\beta/2}}{2\Gamma(1+\beta/2)}\sqrt{\frac{\pi}{B}}, \quad \eta_2(t) \sim \frac{t^{\beta}}{B\Gamma(1+\beta)}, \tag{21}$$

where $\Gamma(z)=\int_0^{\infty} t^{z-1}\mathrm{e}^{-t}dt$ is the gamma function. Equation (11) implies that $\langle L\rangle \sim t^{\beta/2}$ and $\langle \Delta L^2\rangle \sim t^{\beta}$. Thus the growth of the filament can no longer be characterized in terms of the simple deterministic Eq. (1), and fluctuations become significant.

IV. MOTOR-ASSISTED TRANSPORT

We now consider a particular model of particle hopping that relates more directly to motor-assisted transport along a filament [10]. In the case of *Chlamydomonas*, anterograde IFT is driven by a kinesin-based motor complex whereas retrograde IFT is dynein based [8]. For concreteness, we construct the master equation for kinesin-based transport and extract from this the anterograde waiting time density ψ^{+} for the equivalent hopping model. An identical analysis can be carried out for dynein-based transport and the associated retrograde waiting time density ψ^{-}. As in the previous section we set $\psi^{+}=\psi^{-}=\psi$.

A single kinesin motor, which has an approximate step length size $l=10$ nm, typically makes around 100 steps before it unbinds from a microtubule filament [11]. This implies an unbinding probability of $\epsilon_0=1/100$ per step. Given a motor speed $v=2\ \mu\mathrm{m\,s^{-1}}$, the unbinding rate is $\bar{\alpha}_{+} \approx l/(\epsilon_0 v)=0.5\ \mathrm{s^{-1}}$. However, IFT particles are large protein complexes that are probably pulled by several molecular motors simultaneously. Suppose that there are m motors per IFT particle and that each motor has the same unbinding probability ϵ_0. Also assume that the speed of the IFT particle is independent of how many motors are bound to the microtubule, provided at least one is bound. If the motor particles are uncorrelated then the unbinding probability per step is of the order ϵ_0^m and the unbinding rate becomes $\alpha_{+}\sim l/(\epsilon_0^m v)$ [10]. In fact, a more detailed model of cooperative cargo transport by several molecular motors shows that there is a distribution of unbinding rates [12]. We will ignore this additional source of stochasticity here and consider a single effective unbinding rate. The effective binding rate α_{-} of an IFT particle is given by the binding rate of a single motor, since once one motor is bound to the microtubule the particle moves with the speed v. Finally, whenever an IFT particle unbinds from a microtubule, in principle, it can diffuse within the cytoplasm of the cell. However, the presence of several intracellular filaments and organelles strongly restricts the motion of the unbound IFT particle, so that to a first approximation it will stay in close proximity to its point of detachment. Therefore, the motion of an IFT particle is characterized by directed motion along the microtubule interspersed with pauses when it unbinds. The basic model is illustrated in Fig. 3.

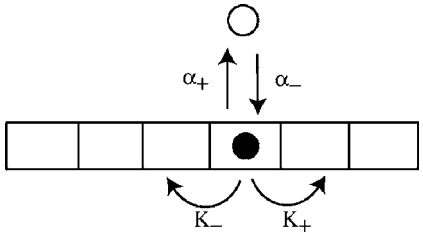

FIG. 3. Two-state particle hopping model. At each lattice site n a particle can undergo transitions between a bound state (filled circle) and an unbound state (unfilled circle) at rates $\alpha_{\pm}$. In the bound state the particle hops to neighboring sites $n\pm1$ at a rate $K_{\pm}$, whereas in the unbound state it is immobile. For anterograde motion $K_{+}=K$, $K_{-}=0$, whereas for retrograde motion $K_{+}=0$, $K_{-}=K$.

Given the above simplifications, we can write down a master equation for motor-assisted transport along a one-dimensional filament track. Since we are interested in extracting the corresponding waiting time density, it is sufficient to consider an infinite lattice. Let $p_n(t)$ be the probability that the particle is at the lattice site n at time t and is in the bound (mobile) state. Denote by $q_n(t)$ the corresponding probability that the particle is in the unbound (immobile) state. Suppose that the particle starts at site $n=0$ in a bound state at time $t=0$. We then have the system of equations

$$\frac{dp_n}{dt} = -\alpha_{+}p_n + \alpha_{-}q_n + K[p_{n-1}-p_n], \tag{22}$$

$$\frac{dq_n}{dt} = -\alpha_{-}q_n + \alpha_{+}p_n, \tag{23}$$

where K is the rate of anterograde hopping (for retrograde hopping $K\to -K$). The initial conditions are $p_n(0)=\delta_{n,0}$ and $q_n(0)=0$. Laplace transforming Eqs. (22) and (23) gives

$$s\hat{p}_n(s) - \delta_{n,0} = -\alpha_{+}\hat{p}_n(s) + \alpha_{-}\hat{q}_n(s) + K[\hat{p}_{n-1}(s) - \hat{p}_n(s)]$$

$$s\hat{q}_n(s) = -\alpha_{-}\hat{q}_n(s) + \alpha_{+}\hat{p}_n(s),$$

which can be solved iteratively to yield the result

$$\hat{p}_n(s) = \frac{1}{K}\left\{\frac{1}{1+\alpha(s)/K}\right\}^{n+1}, \quad \hat{q}_n(s) = \frac{\alpha_{+}}{s+\alpha_{-}}\hat{p}_n(s), \tag{24}$$

where

$$\alpha(s) = \frac{s[s+\alpha_+ + \alpha_-]}{s+\alpha_-} \tag{25}$$

The next step is to reformulate the model in terms of a particle hopping with a waiting time density $\psi(t)$. Let $r_n(t) = p_n(t) + q_n(t)$ be the total probability that the particle is at site n at time t. For this event to occur, the particle has to have made n steps in some time interval $(0,t')$ and then have made no further steps in the interval (t',t). Thus

$$r_n(t) = \int_0^t \psi_n(t')\Psi(t-t')dt', \tag{26}$$

where $\psi_n(t)$ is the probability density for the time of occurrence of the nth step and

$$\Psi(t) = \int_t^\infty \psi(t')dt' \tag{27}$$

is the probability that the particle has not left the nth site at time t. In terms of Laplace transforms,

$$\hat{r}_n(s) = \frac{\hat{\psi}(s)^n\{1-\hat{\psi}(s)\}}{s}. \tag{28}$$

From Eqs. (24) and (25), it can be seen that

$$\hat{r}_n(s) = \frac{\alpha(s)}{sK}\left\{\frac{1}{1+\alpha(s)/K}\right\}^{n+1}, \tag{29}$$

which implies that

$$\hat{\psi}(s) = \frac{1}{1+\alpha(s)/K}. \tag{30}$$

Having obtained the waiting time density, the analysis of Secs. II and III can now be applied. In particular, Taylor expanding Eq. (30) as a power series in s using Eq. (25)

$$\hat{\psi}(s) = 1 - s\frac{\alpha_+ + \alpha_-}{K\alpha_-} + s^2\left\{\frac{\alpha_+}{K\alpha_-^2} + \left[\frac{\alpha_+ + \alpha_-}{K\alpha_-}\right]^2\right\} + \cdots, \tag{31}$$

the mean waiting time distribution for the two state hopping process can be extracted as $\tau = (\alpha_+ + \alpha_-)/K\alpha_-$. This can then be substituted into Eq. (19) to determine the mean rate of growth of the filament in the large-t limit. The relationship between master equations such as (22) and (23) and particle-hopping models with a corresponding waiting time density is of course well known within the context of continuous time random walks [9,13,14]. The major point of our analysis is to show how this can be incorporated into a theory of motor-assisted filament growth. One of the observations that arose in early studies of continuous-time random walks is that when there exist multiple states of a particle arising, for example, from multiple traps, anomalous transport can occur at large but finite times, with normal transport being recovered in the large-t limit [13,14]. It is likely that the complex system of proteins and motors involved in intraflagellar transport also exist in more than two states with different degrees of mobility. Such systems could, therefore, also potentially exhibit anomalous behavior at intermediate time scales. It should be emphasized that experimental observations of IFT particles suggest that their motion is quite regular, at least under normal conditions [8]. However, defects in IFT transport, which are thought to occur in a number of diseases [6] might result in more disordered behavior.

V. FLAGELLAR LENGTH CONTROL

So far we have ignored spontaneous, particle-independent disassembly of a filament, which occurs in intraflagellar transport. Incorporating this into the above analysis is nontrivial, since one now has to keep track of the random times at which the particle returns to the + end *and* the random amount of material lost during each return trip. However, in the case of normal transport, we can determine the balance-point and estimate fluctuations about the balance point using the following approximation. Suppose that $L^* = N^*\ell$ is the equilibrium length of the flagellum. Let $f^*(t)$ be the first passage density for a particle to make one round trip to the + end given the length L^*. In the symmetric case, $f^*(t)$ is given by the inverse Laplace transform of $e^{-2L^*\gamma(s)/\ell}$. We define the balance point to be when the rate of disassembly V times the mean first passage time is equal to the increase $M\ell$ in filament length generated by the IFT particle on each visit to the + end: $V\langle T\rangle = M\ell$, where $\langle T\rangle = \int_0^\infty t f^*(t)dt$. Fluctuations about this equilibrium are then estimated according to $\sigma^2 = V^2\{\langle T^2\rangle - \langle T\rangle^2\}$ with $\langle T^2\rangle = \int_0^\infty t^2 f^*(t)dt$. Both the mean and variance of the first passage times can be extracted from Taylor expanding the Laplace transform of $f^*(t)$

$$\begin{aligned}\hat{f}^*(s) &= \hat{\psi}(s)^{2N^*} \\ &= (1 - \tau s + \hat{\psi}_2 s^2/2 + \cdots)^{2N^*} \\ &= 1 - 2N^*\tau s + (N^*\hat{\psi}_2 + N^*(2N^*-1)\tau^2)s^2 + \cdots.\end{aligned} \tag{32}$$

We have assumed that both the mean and variance of the waiting times are finite. It follows that:

$$\langle T\rangle = 2N^*\tau, \quad \langle T^2\rangle - \langle T\rangle^2 = 2N^*(\hat{\psi}_2 - \tau^2). \tag{33}$$

Thus the expected length at the balance point is

$$L^* = \frac{\ell\bar{v}}{2V}, \tag{34}$$

with $\bar{v} = \ell/\tau$, and the estimated relative size of fluctuations about the balance point is

$$\Delta \equiv \frac{\sigma}{L^*} = V\sqrt{\frac{2(\hat{\psi}_2 - \tau^2)}{\ell L^*}}. \tag{35}$$

In the particular case of the two-state model discussed in Sec. IV, the term $\hat{\psi}_2$ can be obtained from Eq. (31)

$$\hat{\psi}_2 = 2\left(\frac{\alpha_+}{K\alpha_-^2} + \tau^2\right). \tag{36}$$

Substituting into Eq. (35) gives

$$\Delta = \frac{2V}{K\ell}\sqrt{\frac{\ell}{L^*}\left(\frac{K}{\alpha_-}\frac{\alpha_+}{\alpha_-}+\frac{\tau^2K^2}{2}\right)}. \tag{37}$$

Also

$$\bar{v} = \frac{K\ell\alpha_-}{\alpha_+ + \alpha_-}. \tag{38}$$

Under normal conditions, the motion of IFT particles appears processive, which suggests that in the two-state model $A \equiv \alpha_+/\alpha_- \ll 1$ and $B \equiv K/\alpha_- \gg 1$, that is, the particle spends most of its time in the mobile state. Taking $\bar{v} \approx K\ell = 2.5\ \mu$m/s, $L^* = 10\ \mu$m, $\ell = 10$ nm, and $V = 0.01\ \mu$m/s, we obtain the estimate $\Delta \sim 2\times 10^{-4}\sqrt{AB+1/2}$. Thus the relative size of the length fluctuations, which depends on the product AB, is expected to be small. However, defects in IFT transport that result in an increase in the rate α_+ of transitions to an immobile state could lead to a reduced mean velocity $\bar{v}$, a reduction in the length L^* at the balance point and an increase in the relative size of length fluctuations.

VI. DISCUSSION

In this paper we have shown how the stochastic dynamics of intraflagellar transport, an important component of flagellar length control, can be formulated in terms of a first passage time problem. We have derived expressions for the mean and variance of the length during a growing phase, where disassembly is neglected, and estimated the size of fluctuations when the flagellum is at its balance point. It should be possible to measure these fluctuations experimentally, thus providing another test for the IFT model of flagellar length control [4,5]. Although recent experimental studies have obtained results that are consistent with such a model, it is possible that other control mechanisms are involved [15]. For example, there must be some mechanism for regulating the number of IFT particles so that the IFT protein content per flagellum is maintained at a constant, length-independent level. When a flagellum is severed some of these particles are lost and must be replaced in order to recover the original length. Thus the problem of flagellar length control reduces to a counting problem. In our analysis we assumed that there is only a single IFT particle, which would mean that the system only has to detect the presence or absence of the particle following damage.

The presence of more than one IFT particle leads to a potentially interesting extension of our work, namely, incorporating the effects of crowding, which could be important when there are several IFT particles moving on a short flagellum. That is, if the mutual exclusion or hardcore repulsion of the IFT particles is taken into account, then the resulting particle interactions can lead to cooperative effects such as the buildup of traffic jams on the filament. One way to address this issue would be to consider a totally asymmetric exclusion process [16], in which particles can hop unidirectionally to neighboring sites on a one-dimensional lattice, provided that these sites are unoccupied. Recently such an exclusion process has been combined with a kinetic model of binding and unbinding of particles to the lattice, which is directly applicable to the problem of analyzing the unidirectional motion of motor proteins on cytoskeletal filaments [17–19]. One of the difficulties in taking into account exclusion effects in our model is that interactions between the IFT particles means that we can no longer analyze the growth process in terms of an independent sequence of first passage times for a single tagged particle. That is, one has to keep track of all the particles since their motions are correlated.

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