Active Biopolymers Confer Fast Reorganization Kinetics

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(Received 24 October 2010; published 17 November 2011)

Many cytoskeletal biopolymers are ''active,'' consuming energy in large quantities. In this Letter, we identify a fundamental difference between active polymers and passive, equilibrium polymers: for equal mean lengths, active polymers can reorganize faster than equilibrium polymers. We show that equilibrium polymers are intrinsically limited to linear scaling between mean lifetime (or mean first-passage time, or MFPT) and mean length, MFPT $\sim \langle L \rangle$, by analogy to 1D Potts models. By contrast, we present a simple active-polymer model that improves upon this scaling, such that MFPT $\sim \langle L \rangle^{1/2}$. Since, to be biologically useful, structural biopolymers must typically be many monomers long yet respond dynamically to the needs of the cell, the difference in reorganization kinetics may help to justify the active polymers' greater energy cost.

DOI: 10.1103/PhysRevLett.107.218103 PACS numbers: 87.16.Ka, 87.10.Ed, 87.16.ad, 87.16.Ln

Cytoskeletal polymers play a key role in cellular reproduction, locomotion, and transport [1–3]. Biopolymers like actin filaments and microtubules in eukaryotes and FtsZ, MreB, and ParM in prokaryotes grow by accumulating monomers bound to the nucleotide triphosphates ATP or GTP. The monomers hydrolyze these triphosphates to the diphosphates ADP or GDP, consuming energy in an irreversible process and inducing conformational changes that destabilize the polymers. In some cells, cytoskeletal ATP consumption can approach 50% of total cellular ATP consumption [4,5]. What advantage do active polymers offer over passive, equilibrium polymers to justify this costly energy expenditure?

We highlight a fundamental difference between active and equilibrium polymers: active polymers can reorganize faster than equilibrium polymers. Moreover, this difference in reorganization times widens as mean polymer length grows. Since biological structures like mitotic spindles or pseudopods must reach a certain size to accomplish their function yet be quickly deconstructed and reorganized, this intrinsic difference may at least partly justify the active polymers' greater energy cost.

A large class of equilibrium models describes a polymer as an ordered sequence of monomers, each of one of q types (including different conformational states of the same molecule). Monomers can attach, detach, and potentially interconvert among the q types. Interactions between neighboring monomers $\{i, i+1\}$ contribute free energy $J_{\{i,i+1\}}$ to the total free energy of the polymer. Such models can also describe polymers consisting of bundles of k protofilaments, by increasing the number of ''monomer'' types to q^k. These models are generalizations of 1D, q^k-state Potts models [6]. The free energy of an equilibrium polymer in these models scales as the polymer length L for large L, specifically $\mathcal{F} \approx L\lambda_{\max}$, where $\lambda_{\max}$ is the largest eigenvalue of the transfer matrix [7]. Hence, the equilibrium distribution of polymer lengths will be exponential, $p(L) \sim e^{-L/\langle L \rangle}$, with a characteristic mean length $\langle L \rangle = \frac{kT}{\lambda_{\max}}$. Because for large L the free energy effectively depends on only the largest eigenvalue $\lambda_{\max}$, the dynamics are essentially one-dimensional even for polymer bundles. This means that the effective force $-\frac{d\mathcal{F}}{dL} \approx -\lambda_{\max}$ is constant, generating a constant negative-velocity drift in the polymer length, with drift velocity $v_d \propto -\lambda_{\max}$. (Polymers maintain a finite equilibrium distribution because this negative drift is balanced by diffusion and nucleation of new polymers.) Importantly, since the polymer length drifts towards zero at constant negative drift velocity, starting from the nucleation length L_{nucl}, the mean polymer lifetime scales as $\frac{L_{\text{nucl}}}{|v_d|} \propto \frac{1}{\lambda_{\max}} \propto \langle L \rangle$. Thus, the mean polymer lifetime or mean first-passage time (MFPT) scales as the mean length $\langle L \rangle$ for equilibrium polymers. This linear scaling is a fundamental limit for an equilibrium polymer. In order to improve upon it, a biological system must employ active or out-of-equilibrium processes. As an example, we present a simple active-polymer model based on microtubule dynamics that yields MFPT $\sim \langle L \rangle^{1/2}$.

Microtubule growth and disassembly dynamics have been well-studied [8–10]. In microtubules (and ParM), GTP hydrolysis leads to stochastic rapid disassembly of the entire polymer in a process called dynamic instability; the classic experimental results [11] are reviewed in [1]. Recent detailed models aim to explain specific aspects of the experimental data [12–16]. We consider instead a minimal microtubule model [17] that incorporates dynamic instability. Specifically, we model an active polymer as an ordered sequence of monomers, each of which is

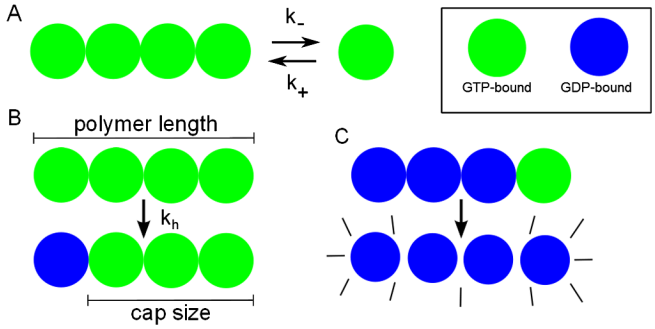

FIG. 1 (color online). Schematic of growth and disassembly of a model active polymer. (a) GTP-bound monomers [light gray (green) circles] bind and unbind at the front end of the polymer. (b) The last GTP-bound monomer at the back of the cap undergoes hydrolysis to become an GDP-bound monomer [dark gray (blue) circles], decreasing the cap size by one. (c) If the cap size shrinks to zero, the polymer completely disassembles.

bound either to GTP or GDP (Fig. 1). We call the group of GTP-bound monomers at the front of the polymer the "cap" and denote its size by x. We denote the total number of monomers (the polymer length) by L. GTP-bound monomers bind and unbind at the front end of the polymer with rates k_+ and k_-, respectively [Fig. 1(a)]. GTP-bound monomers at the back of the polymer cap undergo hydrolysis to become GDP-bound monomers with rate k_h [Fig. 1(b)]. If the cap size shrinks to zero, the polymer completely disassembles [Fig. 1(c)]. New polymers of length and cap size 2 are nucleated with rate k_{nucl}. We call the concentration of free GTP-bound monomers c and analytically treat the mean-field regime where c is constant, a good approximation for eukaryotic cells where the number of monomers is typically large ($\sim 10^6$). For comparison, we also consider an equilibrium polymer that obeys the same rules but without hydrolysis, so that its length and cap size are equal. We show explicitly that this particular equilibrium model satisfies the general equilibrium scaling relation MFPT $\sim \langle L \rangle$.

The exact master equation for the concentration $C_{L,x}$ of polymers of length L and cap size x is

$$\frac{d}{dt}C_{L,x} = k_+ c(C_{L-1,x-1} - C_{L,x}) + k_-(C_{L+1,x+1} - C_{L,x}) + k_h(C_{L,x+1} - C_{L,x}) + k_{\mathrm{nucl}} c^2 \delta_{L,2}\delta_{x,2}. \quad (1)$$

Coarse-graining this equation leads to a continuum Fokker-Planck (FP) description of the probability $p = p(x, L, t)$ that a single active polymer will have length L and cap size x at a time t after its birth:

$$\frac{\partial p}{\partial t} = D\frac{\partial^2 p}{\partial x^2} + D_{LL}\frac{\partial^2 p}{\partial L^2} + D_{xL}\frac{\partial^2 p}{\partial x \partial L} - a\frac{\partial p}{\partial x} - g\frac{\partial p}{\partial L}, \quad (2)$$

where $D = D_{xx} = \frac{1}{2}(k_+ c + k_- + k_h)$, $D_{LL} = \frac{1}{2}(k_+ c + k_-)$, and $D_{xL} = k_+ c + k_-$ are diffusion coefficients; $a = k_+ c - k_- - k_h$ is the cap drift velocity ($a < 0$); and $g = k_+ c - k_-$ is the length drift velocity. The FP equation (2) describes the time evolution of an individual polymer born at time 0 (the time coordinate t represents polymer age). In the mean-field regime, each polymer evolves independently once nucleated, and hence the k_{nucl} term does not appear (for details, see [18]). Assuming $g \gg -a$, the effect of cap diffusion dominates the effect of length diffusion, and so we may neglect the D_{LL} and D_{xL} terms [18]. Solving the FP equation (2) yields

$$p(x, L, t) = \frac{1}{\sqrt{4\pi D t}} e^{[-(x-at-2)^2/4Dt]} \times (1 - e^{(-2x/Dt)})\delta(L - gt - 2), \quad (3)$$

where the initial condition is $p(x, L, 0) = \delta(x-2)\times\delta(L-2)$—i.e., polymers nucleate with length and cap size 2—and the boundary condition is $p(0, L, t) = 0$—i.e., polymers with cap size zero disassemble. (Changing the nucleation size does not affect any essential results.)

The distribution of polymer lifetimes or first-passage times (FPTs) is

$$P_{\mathrm{FPT}}(t) = -\frac{d}{dt}\iint_0^\infty p(x, L, t)\,dx\,dL = \frac{1}{\sqrt{\pi D t^3}} e^{-[(at+2)^2/4Dt]}, \quad (4)$$

and the MFPT has the simple form MFPT $= -2/a$. The steady-state polymer length distribution is

$$P_{\mathrm{active}}(L) = \iint_0^\infty p(x, L, t)\,dx\,dt, \quad (5)$$

yielding the active-polymer average length

$$\langle L \rangle_{\mathrm{active}} = \int_0^\infty P_{\mathrm{active}}(L) L\,dL = \frac{g(D-a)}{a^2}, \quad (6)$$

so that, for long polymers ($\langle L \rangle \gg 1, |a| \ll 1$), one finds $\langle L \rangle \simeq gD/a^2$, and therefore MFPT $= -2/a \sim \langle L \rangle^{1/2}$ to leading order. This sublinear scaling requires some nonequilibrium process, here the irreversible hydrolysis of monomers. Note that the details of the nonequilibrium model do matter to the degree of sublinearity; for example, a more realistic microtubule model [17] yields MFPT $\sim \langle \mathrm{L} \rangle^{0.7}$ [18].

By comparison, in the equilibrium limit of this model, the cap is the entire polymer. Dropping the d/dL terms in (2) yields an equilibrium solution that looks like (3) without the factor $\delta(L - gt - 2)$. The equilibrium length distribution can then be obtained by integrating over polymer age:

$$P_{\mathrm{equil}}(L) = -\frac{a}{D} e^{aL/D}, \quad (7)$$

and the equilibrium-polymer average length is $\langle L \rangle_{\mathrm{equil}} = -D/a$. Hence, we recover the linear scaling MFPT $\sim \langle L \rangle$ expected for equilibrium polymers.

To validate these scaling relations, the master equation (1) was simulated using the Gillespie algorithm [19]. The monomer addition rate k_+ was held fixed throughout the simulations. For equilibrium polymers, we set $k_h = 0$, while, for active polymers, for simplicity, we set $k_- = 0$. The nucleation rate k_{nucl} was tuned to hold the steady-state fraction of polymerized material constant at 75%, with k_{nucl} from 10^{-5} to 10^{-8}. This is in line with experimentally measured values for microtubules [20]. (Changing the fraction of polymerized material to 95% does not affect the qualitative results [18].) This leaves a single free parameter, k_- for equilibrium polymers and k_h for active polymers, to control the polymer length and MFPT. With only a single free parameter, each system is fully constrained by holding either the MFPT or the average length fixed, thus yielding a fair comparison between the equilibrium and active polymers.

Figure 2(a) shows the MFPT of the equilibrium and active polymers as functions of their average length. The data points are from simulations using 400 000 monomers; the curves are from MFPT $= -2/a$ combined with $\langle L\rangle_{\text{equil}} = -D/a$ and (6) for $\langle L\rangle_{\text{active}}$. The MFPT scales $\sim\langle L\rangle$ for equilibrium polymers and $\sim\langle L\rangle^{1/2}$ for active polymers, as expected. Hence, for the same average length, the active polymers have much shorter mean lifetimes than the equilibrium polymers, and this difference widens as average length grows. Figure 2(b) compares length distributions for the equilibrium and active polymers with the same MFPT ($\simeq 10$). Theoretical results from (5) and (7) are shown in solid black lines. Agreement between simulation and theory is excellent, validating our use of the FP equation. (For a comparison of length distributions with the same $\langle L\rangle$, see [18].)

What might be the biological consequences of the different equilibrium- and active-polymer scaling relations? To address this question, we examine the time scale for large-scale spatial reorganization of structures, i.e., the time needed for a system to disassemble polymers at one site, move the material to another site, and reassemble new polymers. Cells often accomplish large-scale polymer reorganization *in vivo* by spatially regulating nucleation [21–23]. To model such regulation simply, we consider two spatial sites. We start simulations with nucleation occurring only at site 1, allow the system to come to a steady state, then switch off nucleation at site 1 and switch on nucleation at site 2. Monomers are assumed to transition between the two sites with a "diffusion" rate k_D, while polymers do not diffuse. We define the "reorganization time" as the time needed after the nucleation switch for 50% of the final steady-state amount of polymerized material to assemble at site 2. Initially, we assume diffusion to be fast ($k_D = \infty$), so that a single effective pool of free monomers is shared between the two sites, and then we consider the more biologically relevant finite-diffusion regime.

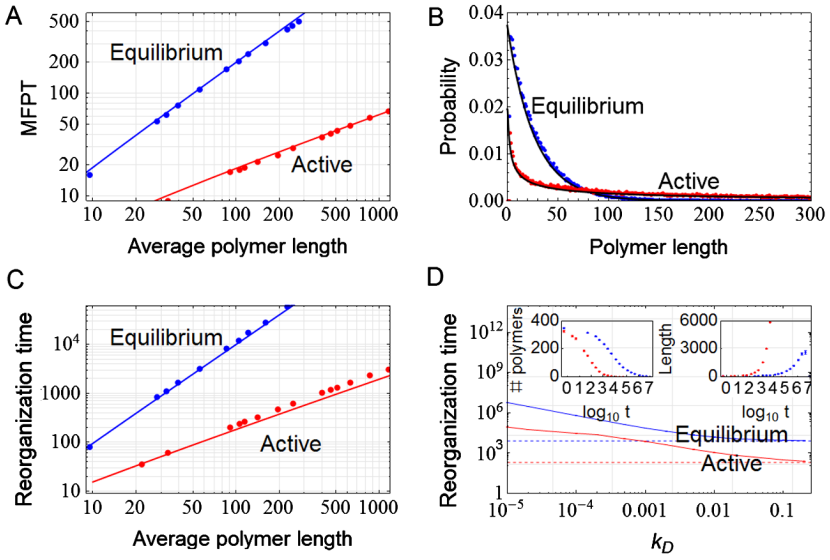

FIG. 2 (color online). Lifetimes versus length for equilibrium [dark gray (blue) lines and dots] and active [light gray (red) lines and dots] polymers. (a) MFPT to polymer disassembly versus average length. The monomer addition rate k_+ is held fixed, and time is always measured in units of $(k_+c)^{-1}$, the mean time for monomer binding. Solid lines are fits to theory with slopes 1 and 0.5 for equilibrium and active polymers, respectively. Some error bars are smaller than data-point symbols. (b) Length distributions with MFPT $\simeq 10$, with theoretical fits (solid black lines) from (5) and (7). The equilibrium polymers have average length 30, while the active polymers have average length 600. (c) Reorganization time (defined in text) versus average length. Solid lines are theoretical fits from (8) with slopes 2 and 1 for equilibrium and active polymers, respectively. (d) Reorganization time versus monomer diffusion constant. Dashed lines show infinite-diffusion limits. Insets: time series showing average polymer number (left) and average polymer length (right) at site 1 versus time after nucleation is switched off.

Figure 2(c) shows the reorganization time for our simple equilibrium and active polymers as functions of their average length, with fast diffusion. The reorganization time scales $\sim\langle L\rangle^2$ for the equilibrium polymers and $\sim\langle L\rangle$ for the active polymers. Hence, for a given average length, the active polymers reorganize faster than the equilibrium polymers, and, like for the MFPT, the difference widens with increasing average length. The scaling exponents differ from those for the MFPT because the reorganization time is dominated by a few very long-lived long polymers, whereas the MFPT is dominated by many short-lived short polymers.

To understand the scaling relations in Fig. 2(c), we estimate the reorganization time analytically as half the ''average material age,'' which we define as the average age of the polymers in a steady-state snapshot of the system, weighted by the length of each polymer:

$$\tau_{\text{reorg}} \approx \frac{1}{2}\frac{\int_0^\infty \text{age}(L)P(L)LdL}{\int_0^\infty P(L)LdL}. \tag{8}$$

This average material age captures the amount of time an average monomer spends in an active polymer before it turns over and well approximates the reorganization time. Long polymers have more material than short polymers, and so the average material age is weighted by the length of each polymer. For our equilibrium polymers, $\text{age}(L) = -L/a$, which gives $\tau_{\text{reorg}}^{\text{equil}} \approx 2D/a^2 \sim \langle L\rangle^2$. Indeed, since the drift velocity $a \sim 1/\langle L\rangle$ for any equilibrium-polymer model as discussed above, $\text{age}(L) \sim L^2$, and thus the equilibrium reorganization time scales generally $\sim\langle L\rangle^2$. As for the MFPT, this scaling is a fundamental property of equilibrium polymers. To improve upon it requires active energy dissipation or some nonequilibrium process. For example, our simple active polymers have $\text{age}(L) = L/g$, and hence $\tau_{\text{reorg}}^{\text{active}} \approx \frac{4(a^2-3aD+3D^2)}{3a^2(D-a)}$, so that, for large $\langle L\rangle$ with $|a| \ll 1$, $\tau_{\text{reorg}}^{\text{active}} \approx 4D/a^2 \sim \langle L\rangle$.

Next, we consider the effects of slow monomer diffusion. Figure 2(d) shows the reorganization time versus the monomer transition rate k_D between sites for equilibrium and active polymers with the same average length ($\simeq 90$) and fraction of polymerized material (75%). The fast-diffusion limits, which are reached for $k_D \simeq 1$ (in units of k_+c), are shown with dashed lines. Strikingly, the active polymers still reorganize much faster than the equilibrium polymers even when slow diffusion limits the reorganization time. To understand this effect, consider the equilibrium-polymer dynamics after nucleation is switched off at site 1: polymers there disassemble stochastically and, since diffusion is slow, the released monomers typically rejoin other polymers at the same site. Hence, the number of polymers at site 1 drops rapidly while the average polymer length grows [Fig. 2(d), insets]. Eventually, site 1 has only a few very long polymers. The equilibrium polymers remain in this state for a very long time, exchanging monomers with the free monomer pool at site 1 while diffusion slowly drains the pool, until the polymers finally disassemble. Therefore, the time needed for slow diffusion to move half the monomers from site 1 to site 2 is a good rough approximation for the equilibrium reorganization time [18]. In contrast, active polymers do not release monomers to the free monomer pool except by disassembly. After the switch in nucleation, the number of active polymers at site 1 drops while the average length grows, similar to the equilibrium polymers. However, the few long-lived active polymers at site 1 then quickly accumulate and hydrolyze all the free monomers there, and then all the polymers disassemble. The time to hydrolyze all the monomers at site 1, plus the time for half of those monomers to diffuse to site 2, is therefore a good rough approximation for the active reorganization time [18].

In summary, we find a fundamental difference between active and equilibrium polymers: active polymers can reach a fixed mean length with faster reorganization kinetics than equilibrium polymers. Very generally, we show that equilibrium-polymer lifetimes scale linearly with mean length. In contrast, active-polymer lifetimes can scale sublinearly, for example, as $\langle L\rangle^{1/2}$ in a simple model motivated by microtubules or as $\langle L\rangle^{0.7}$ in a more realistic model [17,18]. Furthermore, in our example, the kinetic advantage of active polymers persists even for slow monomer diffusion. In a dynamic cellular environment, this kinetic advantage may help justify active polymers' greater energy cost.

Our comparison of active and equilibrium polymers predicts that one might find equilibrium polymers in biological contexts where polymer turnover is slow or structures rarely need to be reorganized. This may be the case for eukaryotic intermediate filaments [24] or for the bacterial homolog crescentin [25]. In addition, the existence of proteins like formins and profilins that accelerate actin polymerization suggests that kinetic regulation of active polymers is important to cells. Finally, although the specific active model we consider is most closely based on polymers like microtubules or ParM that exhibit dynamic instability, our conclusions regarding accelerated kinetics could also relate to actin networks for which branching plays a role analogous to nucleation [26].

Our model neglects many complexities of real biopolymers; clearly, active polymers accomplish more than simply reaching a certain length with a certain lifetime. We only suggest that fast reorganization kinetics might be a general (and generally desirable) feature of the active-polymer systems that are ubiquitous in biology.

We thank William Bialek, Zemer Gitai, Joshua Shaevitz, and Sven van Teeffelen for helpful suggestions. D. S. was supported by the National Science Foundation, and N. S. W. was supported by National Science Foundation Grant No. PHY-0957573.

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