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Motor-mediated alignment of microtubules in semidilute mixtures

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We propose and study a model of molecular motor-induced ordering in a cytoskeletal filament solution for the semidilute case. Motors attach to a pair of filaments and walk along the pair bringing them into closer alignment. In the semidilute regime multiple motors can bind a filament to several others and, for a critical motor density, induce a transition to an ordered phase with a nonzero mean orientation. The motors, on the one hand, cause closer filament alignment, and, on the other hand, induce fluctuations that are dependent on the relative orientation of the filaments to which the motors are attached. We develop a spatially homogenous, mean-field theory that explicitly accounts for a force-dependent detachment rate of motors, which in turn affects the mean and the fluctuations of the net force acting on a filament. This model considers each filament to be in motor contact with all other filaments in the solution. We show that the transition to the oriented state changes from second order to first order when the force-dependent detachment becomes important.

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I. INTRODUCTION

The dynamics and self-organization of the cytoskeleton [1] is an important subject of study in the biological sciences as well as in soft matter physics as a natural realization of an out-of-equilibrium complex fluid. In the presence of the energy source ATP (Adenosine triphosphate), self-organized structures [2–9] and out-of equilibrium fluctuations [10–12] have been observed experimentally as well as in theoretical models.

The essential picture involves interactions between filaments mediated by molecular motors in the following manner. A multiheaded molecular motor (or oligomer comprised of several single-headed motors) attaches to a pair of filaments and, by converting the chemical energy of ATP into mechanical energy, walks along the pair while exerting a force that brings the pair into closer alignment. Examples of such motors include artificial oligomers of kinesin-type [4] or natural bipolar Eg5 motors interacting with microtubules, and myosin minifilaments [5,13] interacting with actin.

In the highly dilute case, binary interactions between motors and filaments are dominant. However, in the semidilute regime multiple motors can bind a filament to several other filaments. When a critical motor density is reached, these interactions induce a transition to an ordered phase with a nonzero mean orientation of filaments—the *isotropic-polar* transition—with the final state referred to as the *self-organized anisotropy*. A complete description of the dynamics remains a formidable task, since it involves nonequilibrium processes, intrinsic nonlinearities, structural anisotropies, and a broad window of time scales, length scales, and densities. For low filament densities, models based on binary rod interactions have been proposed [7,9,14–16], but in reality the cytosol is not sufficiently dilute to justify this approach [17]. Additionally, hydrodynamic models have been formulated [6,18], but their validity is not obvious, and the connections between the phenomenological parameters and the underlying microscopic mechanisms are not yet known.

The structures found experimentally in cytoskeletal solutions, such as asters and vortices, can be interpreted as the topological defects of a homogeneous polar phase [9]. How this polar phase arises out of an isotropic semidilute solution, however, remains an open question. In this study, we try to fill this gap and formulate a model for the semidilute regime in which the filament density is too high for two-particle interaction models to be valid but still below the isotropic-nematic transition occurring for systems of passive anisotropic particles [19]. We use a Landau-Lifshitz-type equation [20] and in our modeling take advantage of knowledge stemming from recently developed models for the alignment of two filaments [21,22]. Since most experimental studies are undertaken in a quasi-two-dimensional setting [4,5], we restrict ourselves to a two-dimensional solution of filaments and motors. Specific effects that are taken into account include angle-dependent noise (due to intrinsic motor force fluctuations) and force-dependent detachment of motors.

We show in a manner similar to the well-studied dilute case that at high enough motor density the network of polar filaments exhibits an orientational transition toward a polar state. In our work, however, we explicitly take into account the specifics of motor dynamics such as force-velocity relations and force-dependent detachment rates. Our main result highlights the importance of the motor attachment dynamics to the type of isotropic-polar transition: without force-dependent detachment the transition is second order, whereas with force-dependent detachment it can be first order. This is in contrast to the usual phase transitions in two-dimensional nematics, which are second order as can be seen from the symmetry arguments of Landau and De Gennes [23]. Our work also illustrates the importance of the intrinsic fluctuations of motor forces (or, "effective temperature") on the macroscopic behavior of motor-filament solutions. We account for the fact that the corresponding effective temperature exceeds the thermodynamic temperature by at least 1

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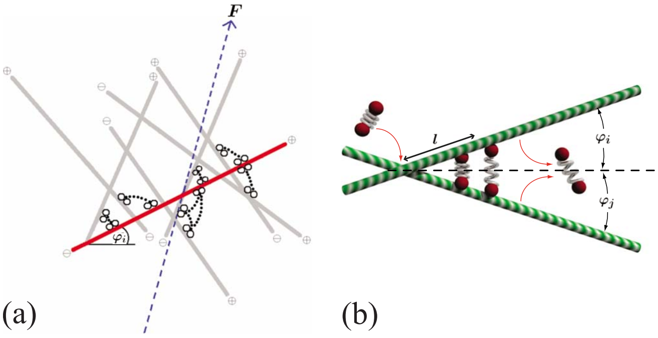

FIG. 1. (Color online) (a) Multirod configuration showing the interaction of the ith microtubule with all other microtubules in the system. The dotted line indicates the direction of forcing due to all binary interactions with the ith rod. (b) Depiction of motor-mediated, binary microtubule interaction. Molecular motors attach at the rod intersection point, zip across the length of the rods causing alignment, and detach.

order of magnitude and that therefore the motor-induced fluctuations should be more important than the thermal fluctuations. In principle, due to its multiplicative nature, motor fluctuations could also promote ordering of filaments for some parameter ranges (in contrast to thermal fluctuations).

The paper is structured as follows. In Sec. II, we discuss the motor-filament interaction rules and develop the governing equations for the spatially homogeneous, motor-mediated self-organization of microtubules. In Sec. III, we discuss the limiting case in which the force-dependent detachment rate is negligible. In this case a parameter-dependent threshold exists above which the isotropic state undergoes a second-order transition to an ordered state. In Sec. IV we show that the inclusion of the force-dependent detachment rate can cause a shift in the transition from second to first order. We conclude in Sec. V with a discussion of results and open questions.

II. MODEL AND ASSOCIATED FOKKER-PLANCK EQUATION

A semidilute solution of microtubules or actin filament bundles interacting via molecular motors is modeled as a collection of N stiff rods of fixed length. In a two-dimensional geometry, the position of each rod can be described by an in-plane vector $\boldsymbol{\tau}_i$, with $i=1,\ldots,N$, or alternatively by the angle φ_i measured with respect to the x axis; see Fig. 1. We want to describe the overdamped dynamics of polar rods that favors their alignment. The Landau-Lifshitz model [20], originally developed to describe the precessional motion of the magnetization in a ferromagnetic solid and augmented by Gilbert [24], captures the universal form of this type of dynamics regardless of its physical origin. According to this model, a rod of orientation $\boldsymbol{\tau}$ relaxes toward a field $\boldsymbol{F}$, which, coupled with the inextensibility requirement (the length of the rod is conserved), leads to the following equation of motion for the ith rod:

$$\zeta_r\dot{\boldsymbol{\tau}}_i=-\boldsymbol{\tau}_i\times(\boldsymbol{\tau}_i\times l_m\boldsymbol{F})-\boldsymbol{\tau}_i\times\boldsymbol{T}, \tag{1}$$

where ζ_r is the rotational drag coefficient and l_m is the average motor run length.

The mean field $\boldsymbol{F}$ represents the average force exerted on the ith filament due to interactions with all other filaments. We intend to study the case of high motor density; hence, for a homogeneous filament solution, each rod is in motor contact with every other rod, and the total number of rods, N, is fixed. $\boldsymbol{T}$ is a thermal noise term given by

$$\boldsymbol{T}=\xi_0\hat{z}. \tag{2}$$

Here ξ_0 is the stochastic torque and $\hat{z}$ is the unit vector perpendicular to the plane of the system. The stochastic force has zero mean, $\langle\xi_0\rangle=0$, (brackets represent the ensemble average), and is assumed to be δ correlated,

$$\langle\xi_0(t)\xi_0(t')\rangle=2k_BT\zeta_r\delta(t-t'), \tag{3}$$

where k_BT is the thermal energy. The stochastic torque, as defined above, gives rise to rotational diffusion with diffusion coefficient $D_r=\frac{k_BT}{\zeta_r}$.

For the field $\boldsymbol{F}$ we use the following form:

$$\boldsymbol{F}=\sum_{j=1}^{N}\boldsymbol{\tau}_j(\sigma\alpha+\xi_j). \tag{4}$$

It is simply the sum of all microtubule interactions with the ith tubule [refer to Fig. 1(a)]. As we do not account for spatial variations, there are $N-1$ interactions. α is the average strength of the motor force and σ is the number of motors per filament pair. The stochastic term ξ_j describes intrinsic fluctuations in the motor forces, and, unlike the thermal noise ξ_0, is multiplicative.

During rod alignment, motors spanning the ith and the jth filaments stretch as they move away from the filament intersection point, exert a force on the ij pair, and experience a corresponding restoring force. When motors attach, they quickly obtain a symmetric orientation perpendicular to the bisecting line of any two interacting rods; see Fig. 1(b). This is due first to the fact that we assume negligible bending rigidity in the spring force which is supported by experimentation [4]. Second, there is a well accepted force-velocity relation [25–27] given by

$$V_M=V\left(1-\frac{F_l}{F_{\mathrm{st}}}\right),$$

where V_M is the motor head velocity, F_l is the projection of the motor spring force on the direction of the rod, and F_{st} is the so-called stall force. Thus, if the motor attaches asymmetrically, the leading motor head (corresponding to the larger distance from the filament intersection point) is slowed down by the spring extension force while the trailing head is accelerated, leading to fast relaxation toward a symmetric configuration.

The number of motors σ_{ij} spanning a filament pair takes the form

$$\sigma_{ij}=\sigma_0\exp\left(-\frac{\kappa al\left|\sin\left(\frac{\varphi_i-\varphi_j}{2}\right)\right|}{k_BT}\right), \tag{5}$$

where σ_0 is the average number of motors per microtubule. The exponential form in Eq. (5) is motivated by experimental studies [28] and was developed in Refs. [29,30]; its effect on the alignment of a pair of filaments by multiple motors was recently studied theoretically in some detail in Ref. [22]. The argument of the exponential represents the ratio of the motor stretching energy to the thermal energy k_BT. The stretching of the motor is expressed by the average distance l (along the microtubule) between the motor position and the intersection point of the two filaments [see Fig. 1(b)] and by the angle between the filaments. κ is the motor spring constant, known to be on the order of $200-400\ \text{pN}/\mu\text{m}$ [31] for kinesin motors, and a is a molecular length scale (a few nm).

The noise terms occurring in the motor force, Eq. (4), are necessary to describe fluctuations in nonequilibrium systems of active motors that can potentially induce an effective temperature larger than the equilibrium (thermodynamic) temperature [10–12,32]. Experiments in actin-myosin mixtures [10] showed strong deviations from thermodynamic equilibrium behavior due to motor fluctuations. We assume $\langle \xi_i(t)\rangle = 0$ and

$$\langle \xi_i(t)\xi_j(t')\rangle = 2\frac{\mu\zeta_r}{l_m^2}\delta(t-t')\delta_{ij}, \tag{6}$$

for $i,j=1,\ldots,N$. The noise amplitude is comprised of $\mu = k_BT_a$, where T_a is the effective (or active) temperature. The effective temperature can be estimated in terms of the mean motor force $\langle F\rangle$, motor step length $\langle L\rangle$, and k_B as $T_a = \frac{\langle F\rangle\langle L\rangle}{k_B}$. Using known experimental values for kinesin-average motor force, $\langle F\rangle = 5$ pN and average motor step length, $\langle L\rangle = 8$ nm [33]—we estimate the effective temperature to be $\simeq 3000$ K (approximately ten times room temperature), which is consistent with [10,11].

If one interprets the components of the orientation vector as the real and imaginary components of a complex number, one can write $\boldsymbol{\tau}_i = e^{i\varphi_i}$ and note the identities $\boldsymbol{\tau}_i \times \boldsymbol{\tau}_j = -\sin(\varphi_i-\varphi_j)\hat{z}$ and $\boldsymbol{\tau}_i \times \hat{z} = -i\boldsymbol{\tau}_i$, where $\hat{z}$ is the unit normal to the plane. The equation of motion can then be written in the following compact Langevin-type form:

$$\zeta_r\dot{\varphi}_i = \alpha\sum_{j=1}^{N}\sigma_{ij}f_{ij} + \sum_{k=0}^{N} f_{ik}\xi_k, \tag{7}$$

with $f_{ij} = -l_m\sin(\varphi_i-\varphi_j)$ and $f_{i0}=1$.

Since we assumed Gaussian white noise, this generalized Langevin equation is stochastically equivalent to a Fokker-Planck equation for the N particle probability density $P^{(N)}(\vec{\varphi})$ with $\vec{\varphi} = (\varphi_1,\varphi_2,\ldots,\varphi_N)$. We interpret the stochastic differential Eq. (7) in the Stratonovich sense. This is the natural interpretation if one assumes, as usually is the case in physical systems, a high frequency cutoff for the spectral density of the noise (see, e.g., [34] for a discussion of multiplicative noise and Ito vs Stratonovich interpretations). One gets

$$\begin{aligned}\frac{\partial}{\partial t}P^{(N)}(\vec{\varphi}) &= \frac{k_BT}{\zeta_r}\sum_{i,j=1}^{N}\frac{\partial^2}{\partial\varphi_i\,\partial\varphi_j}P^{(N)}(\vec{\varphi})\\ &\quad + \frac{\alpha l_m}{\zeta_r}\sum_{i,j=1}^{N}\frac{\partial}{\partial\varphi_i}[\sigma(\varphi_i-\varphi_j)\sin(\varphi_i-\varphi_j)P^{(N)}(\vec{\varphi})]\\ &\quad + \frac{\mu}{\zeta_r}\sum_{i,j}\frac{\partial}{\partial\varphi_i}\left\{\sin(\varphi_i-\varphi_j)\right.\\ &\quad \left.\times\frac{\partial}{\partial\varphi_j}[\sin(\varphi_i-\varphi_j)P^{(N)}(\vec{\varphi})]\right\}.\end{aligned} \tag{8}$$

A mean-field approximation is applied by assuming independence of rods in the following manner: $P^{(N)}(\varphi_1,\ldots,\varphi_N) = P(\varphi_1)P(\varphi_2)\cdots P(\varphi_N)$, where $P(\varphi) = P^{(1)}(\varphi) = \int_{-\pi}^{\pi}P^{(N)}(\varphi,\varphi_2,\ldots,\varphi_N)d\varphi_2,\ldots,d\varphi_N$ is the single-particle distribution function. We now integrate Eq. (8) with respect to the last $N-1$ angle variables. After rescaling $t\mapsto(\tilde{t}\zeta_r)/k_BT$, and defining $\tilde{\alpha} = \frac{\alpha l_m(N-1)}{k_BT}$, $\tilde{\mu} = \frac{\mu(N-1)}{2k_BT}$, $\tilde{\sigma} = \sigma_0\sigma$, and $\tilde{\kappa} = \frac{\kappa a l}{k_BT}$, we obtain the mean-field equation for $P(\varphi)$ (see Appendix A for details; in the following, tildes on scaled quantities are suppressed for brevity):

$$\begin{aligned}\frac{\partial}{\partial t}P(\varphi) &= \frac{\partial^2}{\partial\varphi^2}P(\varphi)\\ &\quad + \alpha\frac{\partial}{\partial\varphi}\int_0^{2\pi}\sigma(\varphi-\varphi')\sin(\varphi-\varphi')P(\varphi)P(\varphi')d\varphi'\\ &\quad - \mu\frac{\partial}{\partial\varphi}[(\gamma\sin 2\varphi - \delta\cos 2\varphi)P(\varphi)]\\ &\quad + \mu\frac{\partial^2}{\partial\varphi^2}[(1-\gamma\cos 2\varphi - \delta\sin 2\varphi)P(\varphi)].\end{aligned} \tag{9}$$

We have introduced $\gamma = \int\cos 2\varphi P(\varphi)d\varphi$ and $\delta = \int\sin 2\varphi P(\varphi)d\varphi$ as abbreviations for the second moments of $P(\varphi)$. The rotational drag coefficient is estimated in [35] as, $\zeta_r \simeq \frac{\pi\eta L^3}{3\ln(L/b)}$, where $L=10-15\ \mu$m is the microtubule length, $b=24$ nm is the microtubule diameter, and $\eta \simeq 0.005\ \text{pNs}/\mu\text{m}^2$ is the solvent viscosity. The time scale associated with thermal fluctuations is computed to be $K_BT/\zeta_r \simeq 3\times 10^{-3}\ \text{s}^{-1}$.

Equation (9) is a nonlinear and nonlocal equation for the probability density of the filament orientations, $P(\varphi)$. It is related to the binary interaction models of Refs. [14] in its incorporation of rotational diffusion due to thermal effects (given by the first term on the right-hand side) and motor-induced interactions (proportional to the renormalized motor strength α). However, previous models assumed *a priori* binary interactions, whereas Eq. (9) is effectively binary explicitly because of the approximation of independence of particles. Moreover, the derivation used here is unique in that it allows straightforward inclusion of the fluctuations in motor force. These are represented by the terms proportional to the renormalized fluctuation strength μ, which should in fact be more important than the thermal effects for realistic conditions.

The uniform density corresponding to $P(\varphi) = P_{\text{iso}} = \frac{1}{2\pi}$ solves Eq. (9) upon application of the normalization condition $\int_0^{2\pi}P(\varphi)d\varphi = 1$. It represents an isotropic distribution of rods. If the ratio of motor-mediated microtubule interaction to diffusion in the system is large enough, the uniform state loses its stability resulting in the onset of spontaneous orientation. In this paper, we study the formation of oriented states in two physical cases. In Sec. III we address the limit of small force-dependent detachment rate, while in Sec. IV we discuss the case of significant detachment rate.

III. SMALL DETACHMENT RATE LIMIT

Motor forcing can be modeled as a single effective spring force independent of the rate at which motors attach and detach. This case is realized when the motor spring strength is small (i.e., $\kappa \ll 1$) or when the angle between interacting rods is small (a limit that has been studied extensively in Ref. [16]). In this limit, there is a constant average number of motors per microtubule, σ_0, and consequently, Eq. (9) simplifies to the following form:

$$\frac{\partial}{\partial t}P(\varphi) = \frac{\partial^2}{\partial \varphi^2}P(\varphi) - \alpha\frac{\partial}{\partial \varphi}[(\bar{\tau}_y \cos\varphi - \bar{\tau}_x \sin\varphi)P(\varphi)] - \mu\frac{\partial}{\partial \varphi}[(\gamma \sin 2\varphi - \delta \cos 2\varphi)P(\varphi)] + \mu\frac{\partial^2}{\partial \varphi^2}[(1 - \gamma\cos 2\varphi - \delta \sin 2\varphi)P(\varphi)], \quad (10)$$

where $\bar{\tau}_x = \int \cos(\varphi)P(\varphi)d\varphi$ and $\bar{\tau}_y = \int \sin(\varphi)P(\varphi)d\varphi$ are the first moments of $P(\varphi)$. Note that Eq. (10) is still nonlinear and nonlocal, since $\bar{\tau}_x$, $\bar{\tau}_y$, γ, and δ are integrals containing $P(\varphi)$.

We now can investigate bifurcations from the isotropic state, $P_{\text{iso}} = \frac{1}{2\pi}$, by doing linear stability analysis. Looking for solutions of Eq. (10) of the form $P(\varphi,t) = \frac{1}{2\pi} + \varsigma(\varphi,t)$, where $\varsigma(\varphi,t)$ is a small perturbation, and choosing $\varsigma(\varphi,t) \propto \exp[\lambda_n t + in\varphi]$ we get the following dispersion relations for the growth rates λ_n of the angular Fourier modes n:

$$|n| = 1: \quad \lambda_1 = \frac{\alpha}{2} - (1+\mu), \quad (11)$$

$$|n| = 2: \quad \lambda_2 = -3\mu - 4, \quad (12)$$

$$|n| > 2: \quad \lambda_n = -n^2(1+\mu). \quad (13)$$

Equations (11)–(13) indicate that perturbations with $n = \pm 1$ grow provided that $\lambda_1 = \frac{\alpha}{2} - (1+\mu) > 0$. This yields a critical α above which the instability occurs,

$$\alpha > \alpha_c = 2(1+\mu). \quad (14)$$

Both rotational diffusion and the motor-induced fluctuations $\propto \mu$ cause the higher harmonics to decay as $-n^2$.

To study the nonlinear dynamics associated with the growth of the first mode close to the instability threshold, one can represent $P(\varphi)$ as the isotropic state plus corrections that evolve on the slow time scale of the growth rate near the threshold,

$$t_\epsilon = \epsilon^2 t. \quad (15)$$

We consider the following expansion:

$$P(\varphi,t) = \frac{1}{2\pi}[1 + \epsilon \tilde{P}_1(\varphi,t_\epsilon) + \epsilon^2 \tilde{P}_2(\varphi,t_\epsilon) + \cdots], \quad (16)$$

with

$$\tilde{P}_k = P_k(t_\epsilon)e^{ik\varphi} + P_{-k}(t_\epsilon)e^{-ik\varphi}. \quad (17)$$

Inserting this expansion into Eq. (10) and collecting coefficients of $e^{ik\varphi}$ yields

$$\epsilon^3 \dot{P}_1 = \epsilon^3\left(\Lambda_1 P_1 - \frac{\alpha}{2}P_2 P_1^*\right) + \epsilon^5 \frac{\mu}{2}P_3 P_2^*, \quad (18)$$

$$\epsilon^4 \dot{P}_2 = -\epsilon^2[P_2(4+3\mu) - \alpha P_1^2] - \epsilon^4 \alpha P_3 P_1^*, \quad (19)$$

where the dot represents the derivative with respect to t_ϵ and $\epsilon^2 \Lambda_1 = \lambda_1$. To leading order in ϵ we get

$$\dot{P}_1 = \Lambda_1 P_1 - \frac{\alpha}{2}P_2 P_1^*,$$

$$0 = -P_2(4+3\mu) + \alpha P_1^2. \quad (20)$$

Solving for P_2 in Eq. (20) leads to a Landau-type equation for the time evolution of the first Fourier mode

$$\dot{P}_1 = \Lambda_1 P_1 - A|P_1|^2 P_1 \quad (21)$$

with

$$\Lambda_1 = \frac{\alpha}{2} - (1+\mu), \quad A = \frac{\alpha^2}{2(4+3\mu)}. \quad (22)$$

Since $A > 0$ holds for all system parameters, the nonlinear term is always stabilizing and Eq. (21) infers that the transition from the isotropic state to the polar oriented state is continuous or second order. In the nomenclature of bifurcation theory it is supercritical. Numerical analysis of Eq. (10) above the stability threshold shows that the isotropic distribution quickly evolves toward a single-peaked stationary distribution, as displayed in Fig. 2(a). This finding is consistent with the well-aligned rod bundles found in previous models based on binary interactions [9,36]. Figure 2(a) was generated using the method of finite differences with parameters $\mu = 3$ (implying $\alpha_c = 8$) and $\alpha = 28$. Figure 2(b) shows the bifurcation diagram for $\alpha > \alpha_c$. The growth of P_1 displayed indicates a continuous transition from the isotropic state ($P = P_{\text{iso}}$ and $P_1 = 0$) to polar alignment $P_1 \neq 0$. The dotted line represents the result from the Landau expansion, while the solid line shows results from numerical integration of the implicit steady-state solution given by Eq. (B3) [the analytical, implicit steady-state solution to Eq. (10) is derived in Appendix B]. As one expects, the Landau equation prediction is good near the threshold and becomes inaccurate with increasing $\alpha - \alpha_c$.

IV. FORCE-DEPENDENT DETACHMENT RATE

The formulation and analysis of Eq. (10) was based on the assumption of a constant average number of motors per filament. In this section, we investigate the more general case in which the force-dependent detachment rate is not negligible. The exponential form of Eq. (5) indicates that the strength of motor-induced interactions is greatly diminished when the angle between interacting rods is large. Hence, one would

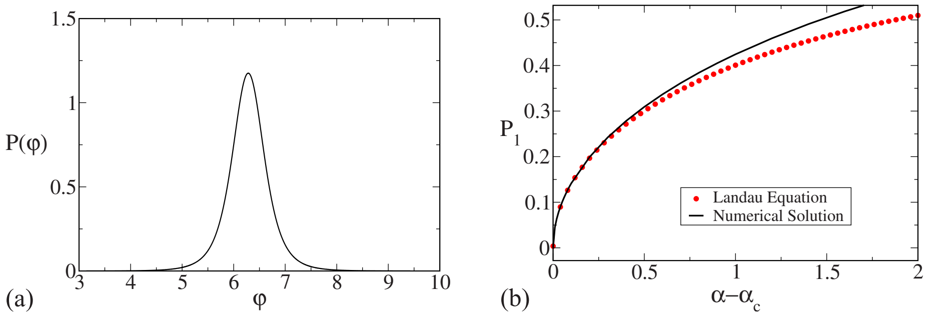

FIG. 2. (Color online) (a) Single-peaked, steady-state distribution solving the small detachment rate master Eq. (10); the parameters used to generate this distribution were $\mu=3$, $\alpha=28$. (b) Bifurcation diagram showing the continuous, supercritical transition to the aligned state. As the theory predicts, the Landau approximation matches well with the numerical data near the stability threshold and departs from it as the magnitude of $\alpha-\alpha_c$ grows.

anticipate the formation of multiple steady-state rod bundles of disparate orientation similar to those found and studied extensively in Ref. [16]. Furthermore, with the inclusion of the detachment dependence, one would expect a more complex transition to alignment due to the nonlocal, motor-induced alignment term, i.e., the term proportional to α in Eq. (9).

The general master equation, given by Eq. (9), is highly nonlinear, and the convolutions in the integral term indicate that analysis is more convenient in Fourier space. Consider the Fourier harmonics of $P(\varphi)$ given by

$$P(\varphi)=\frac{1}{2\pi}\sum_n P_n e^{in\varphi}, \quad P_n=\int_0^{2\pi} P(\varphi)e^{-in\varphi}. \tag{23}$$

Substituting Eq. (23) into Eq. (9) yields equations for the Fourier coefficients P_n,

$$\dot{P}_n=-n^2P_n(1+\mu)+\frac{1}{2}\alpha n\sum_k P_{n-k}P_k(q_{k-1}-q_{k+1}) - \frac{\mu n}{2}(P_{n-2}P_2-P_{n+2}P_{-2})+\frac{\mu n^2}{2}(P_{n-2}P_2+P_{n+2}P_{-2}), \tag{24}$$

where we have defined

$$q_k=\frac{1}{2\pi}\int_0^{2\pi}\exp\left[-\kappa\left|\sin\left(\frac{\varphi}{2}\right)\right|-ik\varphi\right]d\varphi. \tag{25}$$

Now, as in Sec. III, we search for the unstable angular wave modes near the isotropic state. Linearizing Eq. (24) about the isotropic state yields again the growth rates λ_n of the nth angular mode,

$$|n|\neq 2{:}\lambda_n=\frac{\alpha n}{2}(q_{n-1}-q_{n+1})-n^2(1+\mu), \tag{26}$$

$$|n|=2{:}\lambda_{\pm 2}=\alpha(q_{\mp 1}-q_{\pm 3})-4-3\mu. \tag{27}$$

In the case of negligible force-dependent detachment, $q_k=0$ holds with the exception of $q_0=1$ and we regain the result of Sec. III, Eqs. (11)–(13). However, for non-negligible force-dependent detachment, Eqs. (26) and (27) indicate that several modes may lose stability, depending on the magnitude of the motor strength parameter α, the values of the q_k, and the motor noise parameter μ. This was not the case for the limit of small detachment rate, in which only the first mode could lose stability.

Furthermore, one can demonstrate the occurrence of both supercritical and subcritical bifurcations from the isotropic state. This can be motivated by again deriving a Landau equation using the procedure introduced in Sec. III, to get

$$\dot{P}_1=\Lambda_1 P_1 - A|P_1|^2P_1+R, \tag{28}$$

$$A=\frac{\alpha^2(q_0-q_2)(q_{-2}-q_0+q_1-q_3)}{2[\alpha(q_{-1}-q_3)-4-3\mu]}, \tag{29}$$

$$\Lambda_1=\frac{\alpha}{2}(q_0-q_2)-1-\mu, \tag{30}$$

where R represents higher order regularizing terms. These have to be included in the subcritical case $A<0$, where the lowest order nonlinearity of the Landau equation is insufficient to get amplitude saturation. They can be calculated but are not specified here. In Eq. (28), both the instability threshold Λ_1 and the nonlinear Landau coefficient governing whether the transition is supercritical ($A>0$) or subcritical ($A<0$) depend on the values of the q_k. They have to be computed approximately using known parameter estimates. We have $\tilde{\kappa}=\frac{\kappa a l}{k_B T}$. The motor spring constant κ has been measured to be 200–400 pN/μm for kinesin motors [31]. For the molecular length scale a, one usually assumes a few nm [29,30]. The parameter l, which represents the average distance from the point of motor attachment to the filament intersection, can be estimated to be about 100 nm [22]. This indicates that $\frac{\kappa a l}{k_B T}\simeq 5-10$ at room temperature; we use a value of 5.1 to compute the q_k terms and write down the simplified Landau coefficients as

$$A=\frac{1.28\times 10^{-3}\alpha^2}{2(0.352\alpha-4-3\mu)},$$

$$\Lambda_1=0.176\alpha-1-\mu.$$

The coefficient A changes sign depending on the relationship between the motor-induced alignment strength α and the mo-

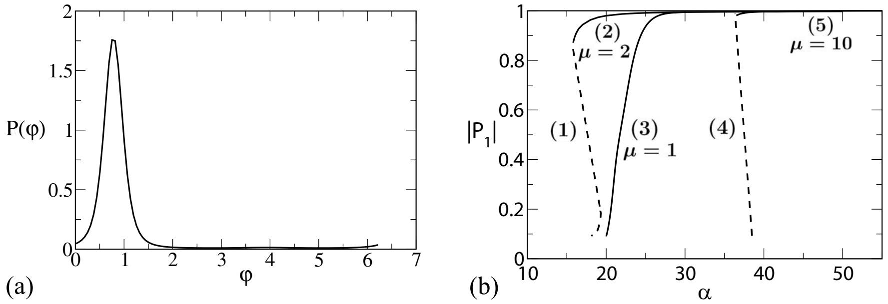

FIG. 3. (a) Steady-state distribution obtained from numerical treatment of Eq. (9) with parameters: $\alpha=16$ $\mu=2$. (b) Bifurcation diagram showing the stable states with nonzero mean orientation associated with the supercritical (3) and subcritical (2) transitions from the isotropic state. The stable branch (5) was calculated for the limiting case of zero diffusion. The dotted branches (1) and (4) show estimates of the repelling branches associated with the subcritical transitions.

tor noise μ. This suggests that there exists a qualitative difference in the transition to alignment depending on the parameter selection, which is supported by numerical simulations of Eq. (9). Figure 3(a) shows a long time oriented state for $\alpha=16$ and $\mu=2$. The peak is steeper, i.e., the orientation is more perfect, as compared to that found in the small detachment rate case. This is caused by the subcriticality. Figure 3(b) shows both a continuous bifurcation as well as a subcritical bifurcation from the isotropic state for fluctuation strengths $\mu=1$ and $\mu=2$, respectively. As a common feature of subcritical transitions, the stable branch below the linear stability threshold indicates a type of hysteresis in which an oriented state exists below threshold, depending on the initial conditions. The subcritical transition for $\mu=10$ was calculated for the limiting case of zero thermal effects (i.e., rotational diffusion $D_r=k_BT/\zeta_r \rightarrow 0$ or $T\rightarrow 0$). As the motor forcing strength is known to be 3–4 times the noise amplitude [33], the following relationship holds for the renormalized parameters: $\alpha \simeq 3\sqrt{\mu}$. We can thus conclude that the limit of vanishing thermal effects is always subcritical for reasonable parameters of κ $(1<\kappa<10)$, α, and μ.

V. CONCLUSIONS

In this paper we presented and analyzed a model for the motor-induced self-organization of microtubules in a semidilute filament solution. Since previous binary interaction models [9,14,16,36] are insufficient in the semidilute limit, we used a mean-field formulation in which any given filament interacts with all other filaments in motor contact. We incorporated both additive noise associated with thermal fluctuations and multiplicative noise describing small scale fluctuations in motor forcing and additionally accounted for force dependence in the detachment kinetics of the motors. With this approach we found that an initially disordered system exhibits an ordering instability resulting in the onset of well-aligned rod bundles, a finding that is consistent with previous binary interaction models.

The structures found experimentally in cytoskeletal solutions such as asters, vortices, etc. are the defects of a homogeneous polar phase [9]. It has been suggested that this polar phase is unstable in spatially inhomogeneous solutions [37]. In our model, however, we study spatially homogeneous interactions and explore the mechanism by which the polar phase arises out of an isotropic semidilute solution. In the present work we were able to show that the isotropic-polar transition can be second or first order, depending on physical quantities such as motor strength, motor number, and motor force fluctuations.

The Fokker-Planck equation derived from the mean-field model for the alignment of rods is discussed in two physical limits. In the case of small detachment rate, we show analytically and numerically that an instability exists if the motor force exceeds a critical value. As a result, the system undergoes a continuous, second-order transition from the isotropic state to the polar aligned state. This type of bifurcation is found in passive liquid crystal systems [23], where, by contrast, the symmetry is apolar. The asymptotic formulation of the Landau equation showed good agreement with the numerical data near the stability threshold. Since motor forces can be significant when many motors are attached to filaments, we accounted also for the more general case of a force-dependent detachment rate of motors. In this case, we showed that first- and second-order transitions to alignment exist when motor forcing dominates random forcing fluctuations. The existence of a subcritical branch is shown to be a function of the motor spring strength and the ratio of motor forcing to motor and thermal noises. At the moment we are not aware of experimental validations for the subcritical scenario. However, our model predicts ordering hysteresis for *in vitro* experiments on alignment dynamics in semidilute and dense solutions of biological filaments.

Several open questions remain. First, the question of when and under which conditions the isotropic-to-polar transition is second or first order should be investigated and clarified experimentally. Second, usually *in vitro* systems display defect structures such as asters and vortices [3–5] as opposed to a homogeneous polar state. In our work, we did not yet consider spatial variations in microtubule or motor density. With the inclusion of spatial inhomogeneity, one could explore the critical parameter space at which the isotropic state loses stability and derive a system of Ginzberg-Landau equations for the mean-field approach, in a similar fashion to Aranson's and Tsimring's [14] binary interaction model. Furthermore, we did not address the dynamics of bundle interaction in the present model. While obtaining a complete description of the underlying orientational dynamics remains a difficult task, a study of long term bundle dynamics is a reasonable endeavor. Previous models of microtubule interaction have shown slow logarithmic coarsening of bundles into fewer orientations [16].

While our analysis is problem specific, we believe that the mean-field approach used in this paper is applicable to many other physical systems in which active interactions promote ordering. A few examples include rod-shaped swimming bacteria or vibrated granular rod systems. Further investigation and modifications of our models could provide deeper insight into other physical processes as well.

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APPENDIX A: FOKKER-PLANCK EQUATION AND EQUATION FOR THE SINGLE-PARTICLE DISTRIBUTION FUNCTION

For the Langevin equation of the form

$$\dot{\varphi}_i = A_i(\vec{\varphi}) + \sum_{k=0}^{N} B_{ik}(\vec{\varphi})\xi_k, \tag{A1}$$

with coefficients, $A_i = \frac{\alpha l_m}{\zeta_r}\Sigma_j \sin(\varphi_i - \varphi_j)\sigma_{ij}$, $B_{ij} = \frac{l_m}{\zeta_r}\sin(\varphi_i - \varphi_j)$, $B_{i0} = \frac{1}{\zeta_r}$, we can write down the Fokker-Planck equation for the N-particle distribution function $P^{(N)}(\varphi_1, \varphi_2, \ldots, \varphi_N)$, in the Stratonovich sense, as

$$\frac{\partial P^{(N)}}{\partial t} = -\sum_{i=1}^{N} \frac{\partial}{\partial \varphi_i}\left[\left(A_i + \frac{1}{2}\sum_{j=1}^{N}\sum_{k=0}^{N} B_{jk}\frac{\partial}{\partial \varphi_j}B_{ik}\right)P^{(N)}\right] + \frac{1}{2}\sum_{i=1}^{N}\sum_{j=1}^{N}\frac{\partial}{\partial \varphi_i}\sum_{k=0}^{N}\frac{\partial}{\partial \varphi_j}[B_{ik}B_{jk}P^{(N)}]. \tag{A2}$$

From Eq. (A2), we derive an equation for the single-particle distribution function $P(\varphi) \equiv P^{(1)}(\varphi)$, which is a marginal of $P^{(N)}$, i.e., $P(\varphi) = \int P^{(N)}(\varphi, \varphi_2, \ldots, \varphi_N)d\varphi_2 d\varphi_3, \ldots, d\varphi_N$. Integrating both sides of Eq. (A2) with respect to the last $N-1$ orientations and imposing periodic boundary conditions leads to

$$\begin{aligned}\frac{\partial P}{\partial t} = {} & \frac{\alpha l_m}{\zeta_r}\int_0^{2\pi}\frac{\partial}{\partial \varphi}\left(\left[\sum_{j=1}^{N}[\sin(\varphi - \varphi_j)]\sigma(\varphi - \varphi_j)\right]P^{(N)}\right)d_2^N\varphi \\ & - \frac{\mu}{2\zeta_r}\int_0^{2\pi}\frac{\partial}{\partial \varphi}\left[\sum_{k=1}^{N}\frac{\partial}{\partial \varphi}\{[\sin(\varphi - \varphi_k)]^2\}P^{(N)}\right]d_2^N\varphi \\ & + \frac{\mu}{\zeta_r}\int_0^{2\pi}\frac{\partial^2}{\partial \varphi^2}\left(\sum_{k=1}^{N}[\sin(\varphi - \varphi_k)]^2 P^{(N)}\right)d_2^N\varphi \\ & + \frac{k_B T}{\zeta_r}\int_0^{2\pi}\frac{\partial^2 P^{(N)}}{\partial \varphi^2}d_2^N\varphi.\end{aligned} \tag{A3}$$

Now we apply a mean-field approximation by assuming independence of particles. Hence, we can write the N-particle distribution function $P^{(N)}$ as a product of single particle functions $P(\varphi)$.

Rescaling $t \mapsto \frac{\tilde{t}\zeta_r}{k_B T}$, and defining $\tilde{\alpha} = \frac{\alpha l_m(N-1)}{k_B T}$, $\tilde{\mu} = \frac{\mu(N-1)}{2k_B T}$, $\tilde{\sigma} = \sigma_0\sigma$, and $\tilde{\kappa} = \frac{\kappa a l}{k_B T}$ yields after some manipulations (tildes are removed for simplicity),

$$\begin{aligned}\frac{\partial P}{\partial t} = {} & \frac{\partial^2 P}{\partial \varphi^2} + \alpha\frac{\partial}{\partial \varphi}\left[\int_0^{2\pi}[\sin(\varphi - \varphi')]\sigma(\varphi - \varphi')P(\varphi)P(\varphi')d\varphi'\right] \\ & - 2\mu\frac{\partial}{\partial \varphi}\left[\left(\frac{\sin(2\phi)}{2}(\overline{\tau_x^2} - \overline{\tau_y^2}) - \overline{\tau_x\tau_y}\cos(2\varphi)\right)P\right] \\ & + 2\mu\frac{\partial^2}{\partial \varphi^2}\{[\cos^2\varphi\,\overline{\tau_y^2} + \sin^2\varphi\,\overline{\tau_x^2} - \sin(2\varphi)\overline{\tau_x\tau_y}]P\}.\end{aligned} \tag{A4}$$

For brevity we have introduced the following abbreviation for the average with respect to $P(\varphi)$:

$$\bar{f} = \int_0^{2\pi} f(\varphi)P(\varphi)d\varphi. \tag{A5}$$

The observable of interest in the state of self-organized anisotropy is the mean orientation $\bar{\tau}$ with components $\bar{\tau}_x$ and $\bar{\tau}_y$ defined as follows:

$$\bar{\tau}_x = \int_0^{2\pi}\cos(\varphi)P(\varphi)d\varphi,$$

$$\bar{\tau}_y = \int_0^{2\pi}\sin(\varphi)P(\varphi)d\varphi. \tag{A6}$$

The other moments occurring are

$$\overline{\tau_x^2} = \int_0^{2\pi}\cos^2\varphi P(\varphi)d\varphi = \frac{1}{2}(1+\gamma),$$

$$\overline{\tau_y^2} = \int_0^{2\pi}\sin^2\varphi P(\varphi)d\varphi = \frac{1}{2}(1-\gamma),$$

and

$$\overline{\tau_x\tau_y} = \int_0^{2\pi}\cos\varphi\sin\varphi P(\varphi)d\varphi = \frac{1}{2}\delta,$$

where $\gamma = \int_0^{2\pi}\cos 2\varphi P(\varphi)d\varphi$ and $\delta = \int_0^{2\pi}\sin 2\varphi P(\varphi)d\varphi$ are the second moments. Substituting the previous definitions into Eq. (A4) gives the dimensionless mean-field equation, Eq. (9), for $P(\varphi)$.

APPENDIX B: IMPLICIT STEADY-STATE SOLUTION FOR THE CASE OF SMALL DETACHMENT RATE

Equation (10), for the case of small detachment rate, can be simplified by rotating the coordinate system so that $\bar{\tau}_y$

$=0$. Numerics indicate that solutions take the form of bumps symmetric with respect to a given φ indicating that solutions are even. Hence, we also make the simplification $\delta=0$. Integrating Eq. (10) for the stationary case results in

$$C = [\alpha \sin \varphi \bar{\tau}_x + \mu\gamma \sin 2\varphi]P + \mu(1 - \gamma \cos 2\varphi + \mu^{-1})\frac{\partial P}{\partial \varphi}. \tag{B1}$$

The integration constant C can be put to zero: if we integrate Eq. (B1) with respect to φ for $\varphi=0,\ldots,2\pi$, the right-hand side vanishes (integrate the second term by parts). Now let $h(\varphi)=\mu(1-\gamma \cos 2\varphi+\mu^{-1})$. Then $h'(\varphi)=\mu(2\gamma \sin 2\varphi)$, and we get

$$0 = \left[\alpha \sin \varphi \bar{\tau}_x + \frac{1}{2}h'(\varphi)\right]P + h(\varphi)\frac{\partial P}{\partial \varphi}. \tag{B2}$$

Equation (B2) can be solved by separation of variables [note that we can divide the equation through by $h(\varphi)$ because $h(\varphi)>0$ for all φ]. Solving for $P(\varphi)$ yields

$$P(\varphi) = \frac{c \exp\left[\frac{\alpha\bar{\tau}_x}{\mu}\frac{\operatorname{arctanh}\left(\frac{2\gamma\cos(\varphi)}{\sqrt{2\gamma(1+\gamma+\mu^{-1})}}\right)}{\sqrt{2\gamma(1+\gamma+\mu^{-1})}}\right]}{\sqrt{1+\mu[1-\gamma\cos(2\varphi)]}}, \tag{B3}$$

where c is a constant of integration that has to be fixed by the normalization condition $\int_0^{2\pi}P(\varphi)d\varphi=1$.

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