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Simple growth models of rigid multifilament biopolymers

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The growth dynamics of rigid biopolymers, consisting of N parallel protofilaments, is investigated theoretically using simple approximate models. In our approach, the structure of a polymer's growing end and lateral interactions between protofilaments are explicitly taken into account, and it is argued that only few configurations are important for a biopolymer's growth. As a result, exact analytic expressions for growth velocity and dispersion are obtained for *any* number of protofilaments and arbitrary geometry of the growing end of the biopolymer. Our theoretical predictions are compared with a full description of biopolymer growth dynamics for the simplest $N=2$ model. It is found that the results from the approximate theory are approaching the exact ones for large lateral interactions between the protofilaments. Our theory is also applied to analyze the experimental data on the growth of microtubules. © *2004 American Institute of Physics.*
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I. INTRODUCTION

Rigid biopolymers such as microtubules, actin filaments, and intermediate filaments are major components of cytoskeleton and cellular environments. They play a fundamental role in biological systems by supporting cellular transport, cell motility, and reproduction.[1–4] Many cellular processes essential for life are driven by polymerization/depolymerization dynamics of these biopolymers. Therefore, a full theoretical description of growth processes is clearly needed in order to understand mechanisms and principles of cell functioning.

Microtubules are rigid, hollow tubular biopolymers made of parallel protofilaments arranged in circular array.[1–3] Each protofilament is a linear polymer chain consisting of alternating α- and β-tubulin subunits. The number of protofilaments varies between 10 and 15 for microtubules from different species, but typically most of them have $N=13$ protofilaments. Lattice structure of microtubules can be viewed as three parallel helices, the so-called three-start helix.[1–3] It also shows a discontinuity or seam, and a functional role of this lattice feature is unknown. The dynamics of microtubules features an unusual phenomenon of alternating between the growing and shrinking phases which is termed dynamic instability. Actin filaments are another example of rigid biopolymers. They can be described as two-stranded helices in which each actin monomer contacts four other monomers, with the strongest interaction along the strands.[1]

Recent experiments[5–8] have provided extensive measurements of growth dynamics of actin filaments and microtubules under the effect of external forces. A number of theoretical models aimed to describe the dynamics of growing rigid biopolymers have been proposed.[9–15] Several studies utilized polymerization ratchet models, which assume that thermal fluctuations at the tip of growing biopolymers control the growth dynamics.[9–12] In these models a rigid biopolymer is viewed as consisting of N independent and *not*-interacting parallel protofilaments. A different approach is to describe the biopolymer's growth dynamics phenomenologically, by considering the overall polymerization and depolymerization processes and neglecting the microscopic details.[13,15] Although current theoretical models provide a reasonable description of many aspects of microtubules and actin filaments growth, there are still many open questions.[13] The general deficiency of current theoretical approaches is the fact that they mainly ignore the microscopic structure and geometrical properties of a biopolymer's lattice, and they also neglect the lateral interactions between protofilaments. Note, however, that in their model of microtubule growth Mogilner and Oster[10] indirectly included the interactions between the protofilaments in the form of a ''subsidy effect.''

The purpose of this article is to investigate the growth dynamics of rigid multifilament biopolymer by taking into account a complex structure of polymer's growing end, its geometrical properties, and interactions between parallel protofilaments. We show that at realistic conditions only a few polymer configurations contribute to the overall dynamics. It allows us to develop a simple approximate one-layer model for rigid biopolymers growth, for which we obtain explicit expressions for velocity and dispersion for *any* number of protofilaments and for arbitrary geometry of the polymer end. The essential issue of this approximate treatment proves out to be an evaluation of analytical expressions for the asymptotic (long-time) mean growth velocity V

$$\langle x(t)\rangle \approx Vt, \tag{1}$$

and for dispersion (or effective diffusion constant) D

$$D \approx \frac{1}{2}\frac{d}{dt}[\langle x^2(t)\rangle - \langle x(t)\rangle^2]. \tag{2}$$

Here, $x(t)$ stands for a coordinate of the biopolymer's tip at time t that grows linearly with time at a stationary-state limit. Dispersion D is a natural measure of fluctuations of growth

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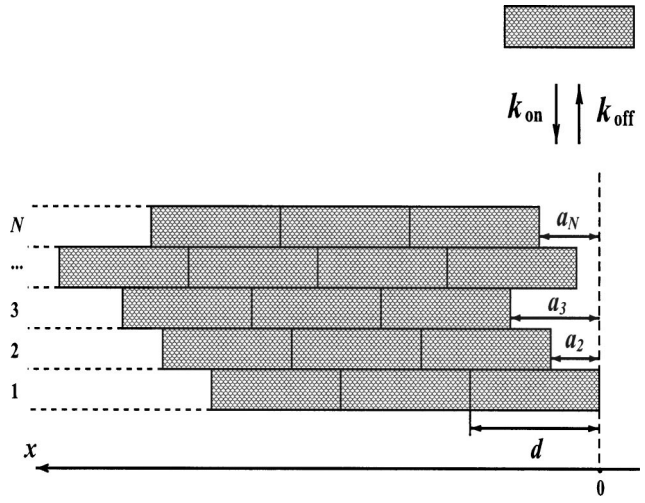

FIG. 1. A typical configuration of growing rigid biopolymer consisting of N protofilaments. The seam in the polymer lattice is between the protofilaments N and 1. The tip of the leading protofilament is at the origin. The free monomer can bind to any protofilament.

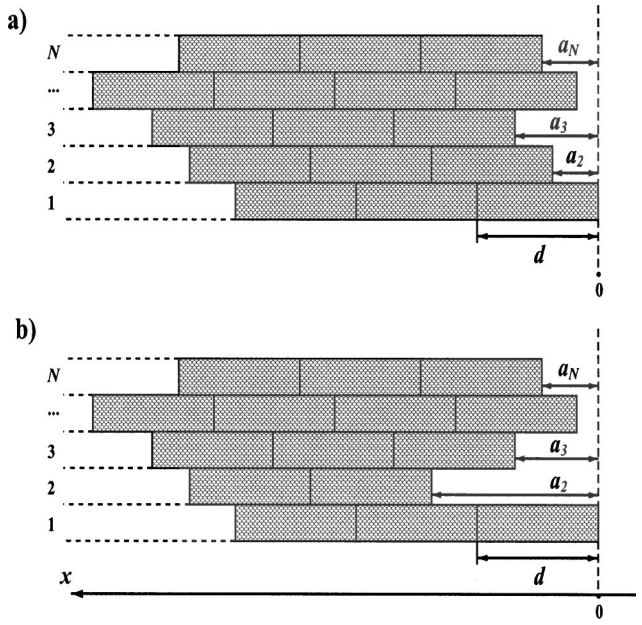

FIG. 2. (a) A biopolymer configuration with all protofilaments at distances less than one subunit length d from the leading protofilament, i.e., a "one-layer" configuration. (b) The biopolymer configuration which is not a "one-layer" configuration. The protofilament 2 is at the distance $a_2 > d$.

dynamics. Note, that although in this article we aim to describe the microtubule dynamics, it could also be used to analyze the growth of other rigid biopolymers, such as actin filaments.

This article is organized as follows: The approximate model of the growth of biopolymer consisting of N protofilaments is presented in Sec. II, while in Sec. III the full description of the growth model with $N=2$ protofilaments is given and compared with the approximate approach. Section IV compares the predictions of the approximate model with the exact growth model for the $N=2$ case, and in Sec. V our theory is used to describe the real experimental data on the growth of microtubules. Section VI summarizes all results and concludes our article.

II. ONE-LAYER MODEL

Consider a growing rigid polymer consisting of N protofilaments as shown in Fig. 1. The building block of such polymers is a monomer subunit of length d. For microtubules this is an α-β-tubulin heterodimer, which has the length of 8.2 nm.[1–3] The protofilaments are parallel to each other but shifted by arbitrary distances. There are chemical interactions between protofilaments that bind them together in a polymer lattice. Protofilaments are labeled in a such way that the seam in the polymer lattice is always between protofilaments 1 and N. There is an infinite number of possible polymer configurations, which can be described by a set of N numbers, $\{a_1, a_2, \ldots, a_N\}$, where a_j is a coordinate of the tip of the protofilament j. For labeling different configurations, let us choose a moving coordinate system where the origin is always at the tip of the leading protofilament, i.e., $a_j=0$ if the protofilament j is the leading one: see Fig. 1.

When a free monomer approaches the growing biopolymer molecule, it can attach to any of the N protofilaments. Define u_j (w_j) as a rate of attachment (detachment) to the protofilament j. These rates are related by the following thermodynamic expression:

$$\frac{u_j}{w_j} = \exp[-(g_v + g_h + g_{im})/k_B T], \tag{3}$$

where g_v is a bond energy due to head-to-tail binding (vertical), g_h is the energy due to lateral (horizontal) interaction, and g_{im} is the free energy of immobilizing the free monomer into the rigid lattice:[17] see Fig. 1. For binding to any protofilament the value of longitudinal energy g_v is the same, however, contributions to the horizontal energy g_h might be different because the local environment of each protofilament tip is different. For polymerization/depolymerization rates we can easily write

$$\begin{aligned} u_j &\propto \exp[-\theta(g_v + g_h + g_{im})/k_B T], \\ w_j &\propto \exp[-(\theta - 1)(g_v + g_h + g_{im})/k_B T], \end{aligned} \tag{4}$$

where the coefficient θ, $0<\theta<1$, reflects the value of the activation barrier for the process of monomer binding. The exact values of the lateral interaction energy g_h for microtubules are unknown, but there is an estimate based on computer simulations of a stochastic model of microtubule assembly dynamics, which gives g_h approximately between -3 and -6 $k_B T$.[18] It is obvious that the monomer could attach much faster to some protofilaments when more lateral bonds are made. That leads to the observation that the growing biopolymer can be found preferentially in some particular configurations. This picture is based on the assumption that the growth of biopolymers is a reaction-limited rather than a diffusion-limited process, which was shown to be correct for microtubule growth in realistic *in vivo* and *in vitro* conditions.[16] This is the basis for our approximate model.

In our model we assume that the growing biopolymer can only be found in configurations with distances from all protofilament tips less than d, i.e., $a_j<d$ for all j, as shown in Fig. 2. It means that all protofilament ends are within one

monomer distance from the leading protofilament. There are N such configurations, because each protofilament can be the leading one only once. This is a *one-layer* model of rigid biopolymer growth.

Consider the dynamics of biopolymer growth in the one-layer model. For the biopolymer in the configuration j, i.e., when the tip of the protofilament j is at the origin, the incoming monomer can only attach to one protofilament, which is the furthest away, and the polymer configuration transformed into another one. The whole new layer of the monomers of length d is added to the biopolymer only when the system goes sequentially through all allowed N configurations, and we return to the same configuration j. Thus, the growing biopolymer advances from the given configuration to the same one, but only shifted by distance d, through the sequence of N states. Then the process repeats again and again. From a mathematical point of view, this dynamic description can be mapped into the motion of a single particle on periodic one-dimensional lattices.[19] Recently, a similar approach has been used successfully to describe the dynamics of motor proteins.[20,21]

This mapping allows us to obtain exact and explicit expressions for the stationary-state growth velocity and the dispersion, or effective diffusion constant, for the rigid biopolymer with *any* number of protofilaments and for any arbitrary set of shifts $\{a_1,a_2,\cdots,a_N\}$ in terms of rates $\{u_j,w_j\}$. The equation for the steady mean velocity of growth is given by[19–21]

$$V=\frac{d}{R_N}\left(1-\prod_{j=1}^{N}\frac{w_j}{u_j}\right), \tag{5}$$

where d is the size of the monomer subunit, while

$$R_N=\sum_{j=1}^{N} r_j, \quad r_j=\frac{1}{u_j}\left(1+\sum_{k=1}^{N-1}\prod_{i=1}^{k}\frac{w_{j+i}}{u_{j+i}}\right). \tag{6}$$

Here we also used the periodicity of the one-layer model, i.e., $u_{j\pm N}=u_j$ and $w_{j\pm N}=w_j$.

The expression for the dispersion is similar but more complex[19–21]

$$D=\frac{d}{N}\left\{\frac{VS_N+dU_N}{R_N^2}-\frac{1}{2}(N+2)V\right\}, \tag{7}$$

where the auxiliary functions are given by

$$S_N=\sum_{j=1}^{N} s_j\sum_{i=1}^{N} i r_{i+j}, \quad U_N=\sum_{j=1}^{N} u_j r_j s_j, \tag{8}$$

with supplementary coefficients

$$s_j=\frac{1}{u_j}\left(1+\sum_{k=1}^{N-1}\prod_{i=1}^{k}\frac{w_{j+1-i}}{u_{j-i}}\right). \tag{9}$$

In the simplest case of the growth of the biopolymer with $N=2$ protofilaments these expressions are reduced to

$$V=d\,\frac{u_1u_2-w_1w_2}{u_1+u_2+w_1+w_2}, \tag{10}$$

for the mean growth velocity, while for the dispersion it yields

$$D=\frac{d^2}{2}\,\frac{u_1u_2+w_1w_2-2(V/d)^2}{u_1+u_2+w_1+w_2}. \tag{11}$$

A. Effect of external loads

Forces produced by growing microtubules are crucial for understanding mechanisms of cellular motility and cellular transport.[1–4] To investigate force production in experiments the growing microtubules are put under external loads which slow down the growth.[5,6] The experimentally used external loads are hard walls and/or optical trap systems. These studies provide valuable information on biopolymer growth mechanisms and cellular motility, and any theoretical description should account for the effect of external forces. In the one-layer model this can be easily done.

Consider a microtubule which is growing against an external force F. This force acts locally only on the leading protofilament. An example will be a hard wall positioned at the tip of the leading protofilament. When a monomer is attaching to the protofilament j, the microtubule produces the work and it is equal to $F(d-a_j)$. Then the rates of polymerization and depolymerization should be modified as follows:

$$\begin{aligned} u_j(F)&=u_j(0)\exp[-\theta_j^{+}F(d-a_j)/k_BT],\\ w_j(F)&=w_j(0)\exp[+\theta_j^{-}F(d-a_j)/k_BT], \end{aligned} \tag{12}$$

where $d-a_j$ is the microtubule length change for monomer binding to the protofilament j, and θ_j^{+} and θ_j^{-} are the *load-distribution factors*. These factors reflect how the external force affects the activation energy for attachment and detachment processes of the monomer subunit.[20,21] Also, the load-distribution factors may have different signs, but we certainly expect that the overall factor

$$\theta=\sum_{j=1}^{N}(\theta_j^{+}+\theta_j^{-}), \tag{13}$$

to equal 1, i.e., positive, implying an opposition to growth of the biopolymer molecule. This simply means that the free energy of the state after adding N subunits differs by Fd from the original state. The force-dependent rate constants can be substituted then in Eqs. (5) and (7) to obtain the load-dependent explicit expressions for the velocity and dispersion, and thus providing a full description of biopolymer growth under external forces.

If the external force opposes to polymerization, then there is a special value of force, termed stalling force, F_S, at which the force-dependent mean growth velocity is approaching zero. This is an important characteristic of real biopolymers.[2] In our approximate model we can easily calculate the stalling force

$$F_S=\frac{k_BT}{d}\ln\frac{\Pi_{j=1}^{N}u_j}{\Pi_{j=1}^{N}w_j}. \tag{14}$$

Similar expressions have been used successfully for the description of motor proteins dynamics.[20–23]

B. Comparison with phenomenological description

It is very interesting to compare our approximate approach with phenomenological models which dominate in the field of microtubule dynamics. According to a phenomenological description, the growth rate is determined by the balance between polymerization and depolymerization processes

$$V=\frac{d}{N}(k_{\mathrm{on}}c-k_{\mathrm{off}}), \tag{15}$$

where c is the concentration of free tubulin subunits, and k_{on} and k_{off} are average rate constants for polymerization and depolymerization, respectively. This simple picture suggests that there is a linear dependence of microtubule growth on tubulin concentration, at least, in the regime where the dynamic instability can be neglected.

In the one-layer model, binding rate constants are also proportional to the concentration of free monomers, $u_j=k_jc$. However, the linear dependence of the mean growth velocity is only valid at large concentrations of monomers, while at low concentrations the behavior is different. The mean growth velocity has a power law dependence on the concentration at this regime. It can be easily seen by analyzing Eq. (10) for the case of the biopolymer growth with $N=2$ biopolymers. At large c, one can obtain $V\propto k_1k_2c/(k_1+k_2)$, while at low c the mean growth velocity has a quadratic dependence. Similar deviations are also found for dispersion as a function of the free monomers concentration. Note that linear behavior is restored when u_j and w_j are equal to u_i and w_i, correspondingly, for all i. However, generally this symmetric situation is not realized since the shifts between the protofilaments are different. We expect that in the general N case the behavior is similar.

The observation that the biopolymer growth velocity may deviate from the simple linear dependence given in Eq. (15) has serious consequences since all experimental measurements have been based on this phenomenological picture. It means that the values of measured rate constants k_{on} and k_{off} may be different for different tubulin concentrations. This could possibly explain a large concentration variability in growth rates of microtubules.[3,24] This question requires a careful experimental investigation.

III. GROWTH DYNAMICS FOR BIOPOLYMERS WITH $N=2$ PROTOFILAMENTS

How well the one-layer model approximates the full growth dynamics of rigid biopolymers is an open question. However, we can answer this question in the simplest nontrivial case of the biopolymer with $N=2$ protofilaments, where an exact solution can be found for the full dynamical description. A comparison between the approximate and the complete dynamical models provides an important physical insight into the mechanism of rigid biopolymer growth, and allows us to understand the applicability of the one-layer model.

When the monomer is binding or dissociating from the growing biopolymer with $N=2$ protofilaments, there are four different situations: see Fig. 3. The monomer can attach

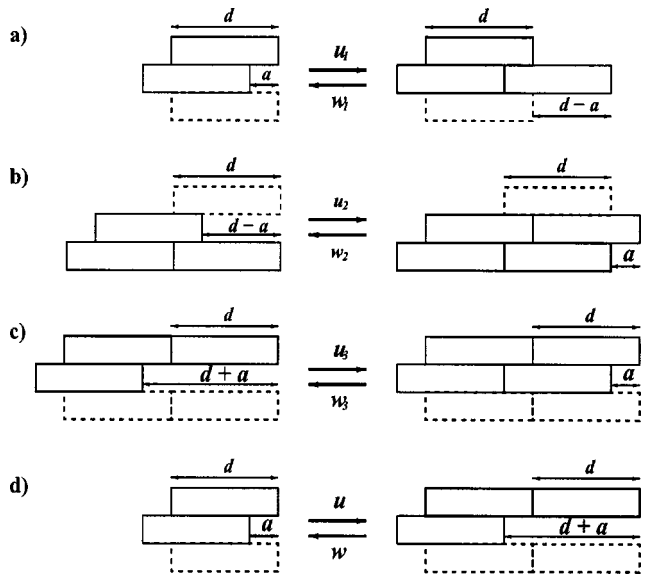

FIG. 3. Four possible situations in the growth of a biopolymer with $N=2$ protofilaments.

with the rate u_1 to the protofilament 1 of the configuration $\{a,0\}$, where a, $0<a<d$, is the shift between the protofilaments, or it can dissociate with the rate w_1 from the protofilament 1 of the configuration $\{0,d-a\}$, as shown in Fig. 3(a). These rates are related through the thermodynamic expression

$$\frac{u_1/c}{w_1}=\exp\left(-\frac{2g_ha/d+g_v+g_{im}}{k_BT}\right), \tag{16}$$

where g_h is the energy of lateral (horizontal) interaction per one subunit, g_v is the longitudinal (vertical) bond energy, and g_{im} is the entropic term which describes the energy of immobilization. Then the factor $2a/d$ gives the fraction of the lateral bond created after the monomer binded to the biopolymer.

Similarly, the monomer can attach with the rate u_2 to the protofilament 2 of the configuration $\{0,d-a\}$, or it can dissociate with the rate w_2 from the protofilament 2 of the configuration $\{a,0\}$, as shown in Fig. 3(b). The relation for these rates is given by

$$\frac{u_2/c}{w_2}=\exp\left(-\frac{2g_h(1-a/d)+g_v+g_{im}}{k_BT}\right). \tag{17}$$

Rates u_3 and w_3 describe the polymerization/depolymerization processes, which do not change the length of the polymer, as illustrated in Fig. 3(c). Meanwhile, the attachment and detachment rates from the leading protofilament for all possible configurations are given by u and w, respectively, as shown in Fig. 3(d). These rates can be described by the following expressions:

$$\frac{u_3/c}{w_3}=\exp\left(-\frac{2g_h+g_v+g_{im}}{k_BT}\right),$$

and

$$\frac{u/c}{w}=\exp\left(-\frac{g_v+g_{im}}{k_BT}\right). \tag{18}$$

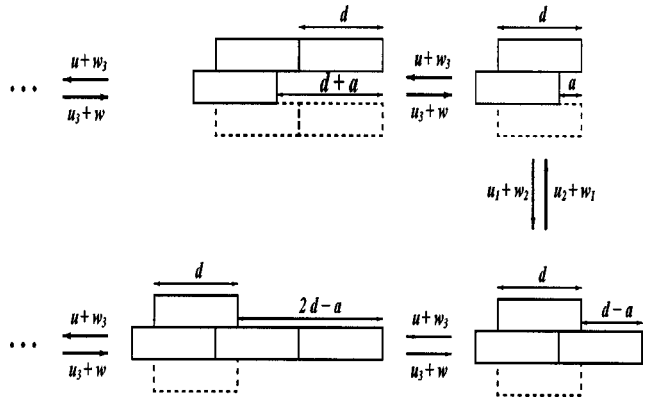

FIG. 4. A kinetic scheme for full dynamics description of the growth of a biopolymer with $N=2$ protofilaments.

For convenience, let us define γ as an energy parameter that specifies lateral interactions,

$$\gamma=\exp(-g_h/k_BT). \tag{19}$$

Then, using Eq. (18), we obtain a set of simpler relations between the rates, namely,

$$\begin{aligned} u_1/w_1&=u/w\gamma^{2a/d},\\ u_2/w_2&=u/w\gamma^{2(1-a/d)},\\ u_3/w_3&=u/w\gamma^2. \end{aligned} \tag{20}$$

Let us define $P(a+id,0)$ as a probability to find the system in a configuration, where the protofilament 2 is the leading one and the tip of the first protofilament is at distance $a+id$, $(i=0,1,...,)$. Similarly, we define $P(0,d-a+id)$ as a probability to find a configuration with the tip of the second protofilament at distance $d-a+id$, $(i=0,1,...,)$ from the tip of the first protofilament, which is now the leading one. The overall kinetic scheme of the system is shown in Fig. 4. Because of the symmetry, at stationary state the overall flux through the system is equal to zero. Then the following relations for probabilities are valid:

$$P(a+id,0)=\left(\frac{u+w_3}{u_3+w}\right)^i P(a,0), \tag{21}$$

$$P(0,d-a+id)=\left(\frac{u+w_3}{u_3+w}\right)^i P(0,d-a), \tag{22}$$

$$P(0,d-a)=\frac{u_1+w_2}{u_2+w_1}P(a,0), \tag{23}$$

with a normalization condition

$$\sum_{i=0}^{\infty}[P(a+id,0)+P(0,d-a+id)]=1. \tag{24}$$

It can be argued that the parameter $(u+w_3)/(u_3+w)\equiv\beta$ is less than 1. This follows from the observation that $u_3>u$ and $w_3<w$, i.e., the monomer binds faster and stronger to interior of the polymer than to the tip of the leading protofilament. After summation of geometrical series in Eqs. (21) and (22), we obtain

$$P(a,0)=\frac{1-\beta}{1+\alpha} \quad \text{and} \quad P(0,d-a)=\frac{\alpha(1-\beta)}{1+\alpha}, \tag{25}$$

where we also defined

$$\alpha=\frac{u_1+w_2}{u_2+w_1}. \tag{26}$$

It is interesting to note that $1-P(a,0)-P(0,d-a)$ gives the fraction of configurations that are neglected in our approximate one-layer model. Using Eqs. (25), the simple calculation for this quantity yields β.

The mean growth velocity can be written as a sum of several terms, namely,

$$\begin{aligned} V=&du+(d-a)u_1P(a,0)+au_2P(0,d-a)\\ &-dw[1-P(a,0)-P(0,d-a)]\\ &-(d-a)w_1P(0,d-a)-aw_2P(a,0). \end{aligned} \tag{27}$$

The first positive term corresponds to adding a monomer to the leading protofilament and increasing the length of the polymer by d. This may take place at any polymer configuration. The second and third positive terms reflect the addition to ''one-layer'' configurations, i.e., where tips of protofilaments are at the distances less than d from each other. Similarly, the first negative term gives the contribution from dissociation of the monomer from the leading protofilament. It shortens the polymer by distance d for all configurations except ''one-layer'' configurations. The last two terms represent negative contributions to the mean growth velocity from the ''one-layer'' configurations.

Substituting expressions (25) into Eq. (27) yields the final expression for the mean growth velocity of the rigid biopolymer with $N=2$ protofilaments

$$V=d\left\{u-w\beta+(1-\beta)\frac{u_1u_2-w_1w_2}{u_1+u_2+w_1+w_2}\right\}. \tag{28}$$

Similar calculations can be performed for the dispersion, or effective diffusion constant.

In the ''one-layer'' model for biopolymer growth with $N=2$ protofilaments, there are only two configurations, $(a,0)$ and $(0,d-a)$. The system can transfer from the configuration $(a,0)$ to the configuration $(0,d-a)$ with the rate u_1+w_2, or it can go backward with the rate u_2+w_1. At $t\to\infty$, the probabilities to find the system in different configurations can be easily calculated to give

$$P(a,0)=\frac{1}{1+\alpha}, \quad \text{and} \quad P(0,d-a)=\frac{\alpha}{1+\alpha}. \tag{29}$$

These equations can also be obtained from the general expressions (25) for the full dynamic case when $\beta=0$, i.e., when we neglect all configurations except ''one-layer'' configurations. Then the mean growth velocity can be easily calculated as follows:

$$V=d\frac{u_1u_2-w_1w_2}{u_1+u_2+w_1+w_2}. \tag{30}$$

Now, we can compare the predictions of the full dynamics and ''one-layer'' $N=2$-model for different values of the

parameter γ, which reflects the energy of lateral interactions between the protofilaments. We can rewrite the thermodynamics expressions (20) in the following form:

$$u_1 = u\gamma^{f_1+a/d}, \quad u_2 = u\gamma^{f_2+(1-a/d)}, \quad u_3 = u\gamma^{f_3+1},$$
$$w_1 = w\gamma^{f_1-a/d}, \quad w_2 = w\gamma^{f_2-(1-a/d)}, \quad w_3 = w\gamma^{f_3-1}. \tag{31}$$

Coefficients f_1, f_2, and f_3 reflect the different values of activation energies for specific polymerization and depolymerization processes. These coefficients may be realistically estimated as

$$-a/d < f_1 < a/d,$$
$$-(1-a/d) < f_2 < (1-a/d), \quad -1 < f_3 < 1. \tag{32}$$

It means that the monomer attaches faster to the place where the stronger lateral bond is created. Similarly, the dissociation is slower if a stronger lateral bond should be broken.

For illustration purposes only, we consider the case when $f_1 = f_2 = f_3 = 0$. The calculations for other possible values of parameters f_1, f_2, and f_3 produce qualitatively similar results. For the model with full dynamics we obtain the following expression for the mean growth velocity:

$$V = d\left(u - \frac{w}{\gamma}\right)\left(1 + \frac{\gamma-1}{\gamma}\frac{\gamma^{a/d}}{1+\gamma^{2a/d-1}}\right). \tag{33}$$

In the ''one-layer'' model the velocity is given by

$$V = d\left(u - \frac{w}{\gamma}\right)\frac{\gamma^{a/d}}{1+\gamma^{2a/d-1}}. \tag{34}$$

To compare theoretical predictions it is convenient to analyze the ratio of velocities, which gives us a measure of deviations between approximate and exact approaches.

For the ratio of growth rates in two models we obtain

$$\frac{V_{\text{one-layer}}}{V_{N=2}} = \frac{1}{1+\gamma^{-a/d}+\gamma^{a/d-1}-\gamma^{-1}} \Rightarrow \begin{cases} \frac{1}{2}, & \gamma = 1 \\ 1, & \gamma \gg 1. \end{cases} \tag{35}$$

The ratio of velocities for two models is also plotted in Fig. 5 for different values of a/d. The simple analysis indicates that for any values of shift between the protofilaments the ratio of velocities is approaching 1 for large γ. The convergence is better with increasing values of a/d and reaches the maximum for $a/d = 0.5$, i.e., when protofilaments are shifted by half the subunit length. But even for relatively small shifts, $a/d = 0.1$, and realistic values of $\gamma \simeq e^{10}$ (energy of lateral interaction between protofilaments is of the order $10k_BT$), the deviation of the approximate ''one-layer'' model from full dynamics description is less than 10%. Thus the ''one-layer'' model provides a very good approximation for the full dynamics description of the growth of rigid biopolymer with $N=2$ protofilaments.

A similar microtubule growth model with $N=2$ protofilaments has been considered earlier,[13] which also gives explicit expressions for mean growth velocity and for the dispersion. However, this model only takes into account the geometrical properties and it mainly neglects the interactions between the tubulin subunits.

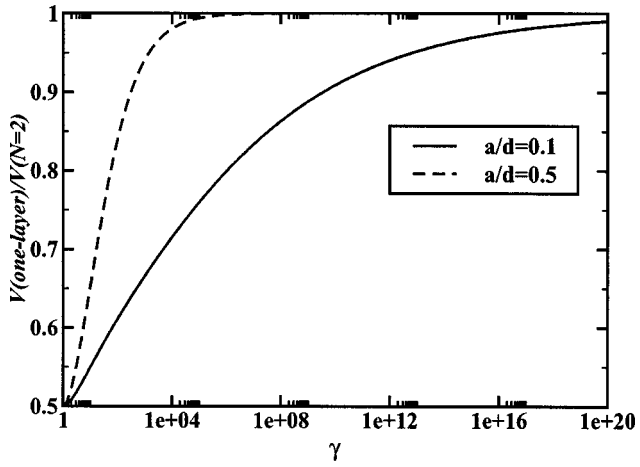

FIG. 5. Ratio of mean growth velocities as a function of the parameter γ for different protofilament shifts within $N=2$ model.

IV. APPLICATION OF THE ONE-LAYER MODEL FOR THE DESCRIPTION OF EXPERIMENTS ON MICROTUBULE GROWTH

It is reasonable to use the ''one-layer'' model to describe the growth of microtubules. The comparison between our approximate results and full dynamics description for $N=2$ model suggests that the ''one-layer'' picture works much better, if the shift between the protofilaments is close to the idealistic symmetric case without seam, i.e., $a = d/N$. In real microtubules the shift between the protofilaments is equal to $a = 0.95$ nm, which is relatively close to the distance $d/13 = 0.63$ nm, which justifies the application of the ''one-layer'' approximate approach. To illustrate our method, we apply the approximate theory to describe the experimental data of Dogterom and Yurke.[5] In these experiments, the growing microtubules encountered a rigid microfabricated barrier, and the external forces have been calculated from buckling shapes of biopolymers for different growth velocities.

To describe this experimental force-velocity relation we used the following parameters: The rate u for the process of association of a tubulin subunit to the tip of the leading protofilament with a creation of the longitudinal (vertical) bond only, the constant w for the dissociation process from the leading protofilament which only breaks the longitudinal bond [see Fig. 3(d) for the biopolymer with $N=2$ protofilaments]; the set of load distribution factors θ_j, $1 \leqslant j \leqslant 13$; and the free energy of creation of lateral (horizontal) bond, g_h. All rates u_j and w_j can be expressed in terms of u, w, and the parameter $\gamma = \exp(-g_h/k_BT)$. To simplify the analysis, we also assumed that all load distribution factors are equal except θ_1 and θ_{13}. It reflects the fact that external force may affect differently the rates of removing or adding a subunit at the two adjacent protofilaments located at the seam.

The growth velocity has been calculated using Eqs. (5) and (6). The effect of external forces has been taken into account by using expressions (12). The rates u_j and w_j have been expressed in terms of rates u, w, and the parameter γ in a way similar to $N=2$ case. The resulting force-velocity curve is shown in Fig. 6. We find that the parameters

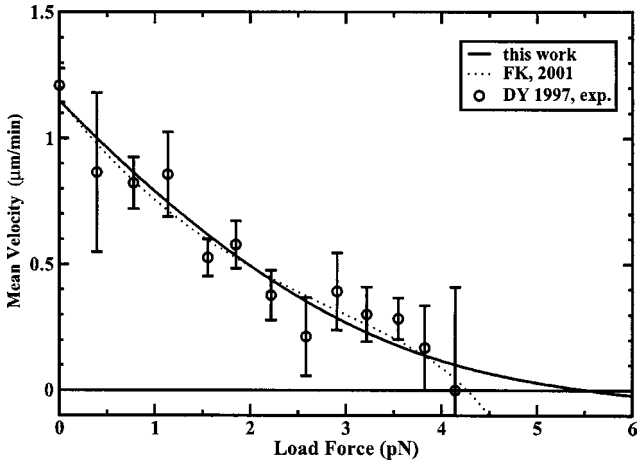

FIG. 6. The force-velocity curve from the experimental data of Dogterom and Yurke (Ref. 5). The solid line represents the fit obtained using the "one-layer" model with load-dependent rate constants. The dotted line is the fit obtained via phenomenological description (Ref. 13).

$$u=8.3\ \mathrm{s}^{-1},\quad w=355\ \mathrm{s}^{-1},\quad \theta_j=1\ \text{ for all }\ j,\quad \gamma=100, \tag{36}$$

provide a very satisfactory optimal fit to the Dogterom and Yurke experimental data. Furthermore, this fit via the relation (14) allows us to predict the stall force $F_S\simeq 5.5$ pN.

As was explained above, our theoretical method also provides a connection with a phenomenological description. From the experimental fit we calculated the rates k_{on} and k_{off}, which are observable rates of polymerization and depolymerization. Because the individual rates of association depend on concentration of free tubulin molecules, $u_j=k_j c$, at the limit of very large concentrations the mean growth velocity in the one-layer model is a linear function. This allows us to estimate k_{on} and k_{off} as follows:

$$k_{\mathrm{on}}=N\Big/\sum_{j=1}^{N} k_j^{-1},\quad \text{and}\quad k_{\mathrm{off}}=k_{\mathrm{on}}c_e, \tag{37}$$

where c_e is the critical concentration of tubulin monomers below which the biopolymer growth cannot happen. It can be easily calculated from Eq. (5), $c_e=[\Pi_{j=1}^{N} w_j/k_j]^{1/N}$. For experimental conditions of Dogterom and Yurke[5] it is given by $c_e\simeq 10.6\ \mu$M, which is only slightly larger than 2–5 μM, obtained in other experiments on microtubule assembly.[25] Calculations from the experimental fit yields the following values for phenomenological rates:

$$k_{\mathrm{on}}=3.0\ \mathrm{s}^{-1}\,\mu\mathrm{M}^{-1}\quad \text{and}\quad k_{\mathrm{off}}=31.8\ \mathrm{s}^{-1}. \tag{38}$$

These estimates are in good agreement with independent experimental observations, which put k_{on} in the range of 2–10 $\mathrm{s}^{-1}\,\mu\mathrm{M}^{-1}$, while the experimental spread for k_{off} is much larger, between 0.1 and 45 s^{-1}.

It is interesting to compare our results with the description of microtubule growth under external force using the phenomenological approach.[13] Kolomeisky and Fisher[13] successfully fitted the experimental data of Dogterom and Yurke with rate constants consistent with experimental bounds and with the prediction of stall force $F_S\simeq 4.3$ pN (see Fig. 6), which is slightly smaller than our results. Also, the dispersion of the growing microtubule was calculated explicitly. However, this description contradicts the thermodynamic conclusions of the simple phenomenological approach, otherwise unphysical negative rate constants for depolymerization are predicted.[5] As a result, Kolomeisky and Fisher[13] concluded, that the stalling state does not represent a thermal equilibrium. The "one-layer" model easily removes this contradiction by taking into account the interactions between the tubulin subunits. Thus, we conclude that when the growth velocity as a function of external forces goes to zero, the system is approaching a thermodynamic equilibrium.

The "one-layer" model incorporates many microscopic properties of microtubules and it allows us to estimate some thermodynamic and structural properties of these biopolymers. The parameter γ is associated with the lateral energy of interaction between the protofilaments. From the fits to experimental measurements we conclude that this energy is given by $g_h\simeq -5k_BT$, which is in excellent agreement with the only available estimates of $-(3.2-5.7)k_BT$, obtained from computer simulations of the stochastic model of microtubule assembly dynamics.[18] Note, however, that reasonable fits could also be produced with values of γ ranging from 10 to 10^4.

Meanwhile the ratio of rates u/w provides information on the energy of longitudinal bond in microtubules. At standard conditions (1 M solution of tubulin) this energy can be calculated from

$$g_v=-k_BT\ln\frac{u/c}{w}-g_{im}, \tag{39}$$

where $c=25\ \mu$M is the concentration of free tubulins in experiments of Dogterom and Yurke.[5] The parameter g_{im} is a standard free energy of immobilization of a tubulin subunit in the polymer lattice, which was estimated to be in the range of $12-18k_BT$.[17] Then, using the fitted values of rates u and w we obtain that $g_v\simeq -(19-25)k_BT$. It is interesting to note that longitudinal interactions in microtubules are much stronger than the lateral interactions between the protofilaments. These estimates are in excellent agreement with results of computer simulations of stochastic models of microtubule growth.[18]

V. SUMMARY AND CONCLUSIONS

We constructed a simple stochastic microscopic model of the growth of rigid multifilament biopolymers. It was argued that association/dissociation rates of individual monomers depend strongly on local environment, which leads to the conclusion that there is a finite number of polymer configurations that specify the dynamics of growing biopolymers. We suggested that most relevant configurations have protofilaments at distances less than a monomer length from each other, i.e., "one-layer" configurations. As a result, the mean growth velocity and dispersion, or the effective diffusion constant, was calculated exactly for any number of protofilaments and for any shifts between them in terms of rate constants for attachments and detachments. It should be noted that simultaneous knowledge of the velocity and dispersion provides a better description of fluctuations and vari-

ability in biopolymer dynamics. Precise experimental measurements of these properties would provide a valuable information on the growth mechanisms.

Our approximate theoretical approach easily takes into account the effect of external forces on growing biopolymers. It could be done by modifying rate constants using chemical-kinetic arguments. It allowed us then to construct a force-velocity relation and to estimate the stalling force, i.e., the force when the growth velocity becomes zero. It was suggested that the comparison with experimental force-velocity curves would provide a testing ground for this theoretical method.

Explicit expressions for the mean growth velocity and for dispersion obtained in the ''one-layer'' model allowed us to investigate the dependence of growth processes on monomers concentration. It is found that at large concentrations the mean growth velocity grows linearly, in agreement with phenomenological descriptions. However, at low concentrations the significant deviations from linearity may be found for some sets of parameters. This observation contradicts the main result of phenomenological models which assume that linear dependence of the growth velocity is valid at all concentrations. These nonlinear deviations are probably due to the fact that the ''one-layer'' model provides a more realistic microscopic description of structural and geometrical properties of growing biopolymers, which apparently is more important at low concentrations of monomers. This question requires careful experimental and theoretical tests.

The validity and applicability of the ''one-layer'' model was discussed for the simple case of the growth of biopolymers with $N=2$ protofilaments. For this case an exact solution for full dynamics that accounts for all possible polymer configurations, was derived. It is found that the predictions of the approximate theory for the mean growth velocity are approaching the exact values for large, but realistic values of lateral interactions between the protofilaments. This indicates that the ''one-layer'' model probably captures main physical and chemical properties of complex growth processes, and it can be used to describe real systems, such as microtubules and actin filaments.

The ''one-layer'' model was used to describe successfully the experiments on microtubule growth under external loads conditions. This approach allowed us to clarify the contradictory statements about the stalling state obtained by different phenomenological models. It was finally concluded that this state corresponds to thermal equilibrium. In addition, the fitting of experimental results allowed us to calculate the lateral and longitudinal energies of interactions between tubulin subunits in the microtubule lattice, which are in excellent agreement with existing estimates.

The advantages of using the ''one-layer'' model to describe the growth of rigid biopolymers is not only its simplicity and the ability to obtain explicit expressions for dynamic parameters, but also its good flexibility and the fact that it can be extended and modified in several directions in order to describe these complex processes more realistically. First, more polymer configurations may be included by considering a ''two-layer'' condition, i.e., that the protofilaments in relevant configurations are at distances less than two monomer subunit lengths. More layers can be added in a similar fashion if required. Thus the results can be improved iteratively, i.e., this extension is analogous to a series expansion approach to the full dynamics description. Second the apparently weaker interactions at the polymer lattice seam can be also incorporated. It will be interesting to know how this addition will effect the growth dynamics. Another possibility is to include tubulin hydrolysis in growth dynamics. This may give a route to investigate the dynamic instability phenomena, which is still the most outstanding problem in the microtubule dynamics. Also, it will be interesting to compare the ''one-layer'' model with computer simulations of microtubule dynamics, which we plan to do in a future work.

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