Packing defects and the width of biopolymer bundles

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The formation of bundles composed of actin filaments and cross-linking proteins is an essential process in the maintenance of the cells' cytoskeleton. It has also been recreated by in-vitro experiments, where actin networks are routinely produced to mimic and study the cellular structures. It has been observed that these bundles seem to have a well-defined width distribution, which has not been adequately described theoretically. We propose here that packing defects of the filaments, quenched and random, contribute an effective repulsion that counters the cross-linking adhesion energy and leads to a well-defined bundle width. This is a two-dimensional strain-field version of the classic Rayleigh instability of charged droplets.

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Filamentous biopolymers, such as F-actin, have the ability to cross link into a variety of bundles and networks, forming the cytoskeleton. The distribution of the radii of cross-linked actin bundles is a basic characteristic that determines the mechanical properties of the cytoskeleton. The thickness of bundles similarly determines the mechanical properties of artificial networks that form in vitro [1–3]. The aggregation of long filaments into bundles has been theoretically investigated, and recently observed experimentally. While equilibrium theory predicts a global phase separation and the formation of a single bundle of infinite width and length [4] (in an infinite system), the observed bundles are limited in thickness [5]. More recently, in-vitro experiments [6] indicate a broad distribution of radii, with a distinct peak and a long tail. The mechanism that is responsible for the observed distribution of finite bundle sizes is not fully understood at present. Several possibilities have been proposed to explain the observed distribution; When the bundles form due to multivalent ions, electrostatic interactions are unbalanced and can lead to a selection of an equilibrium finite radius [7]. A recent study attributes the finite size of the actin bundles to the inherent chirality of the packing of actin filaments [8]. The individual filaments progressively twist over the entire bundle circumference, and the strain energy involved in this global twist limits the growth of the bundle thickness. These effects may indeed be dominant when the filaments are linked by small multivalent ions [9–11]. On the other hand, actin bundles can be more strongly chemically cross linked by larger proteins [2,3,5,6]. In these cases the chirality of the individual filaments and electrostatic interactions may play a lesser role.

We present here a simple analysis of the energetics of a bundle of neutral, achiral filaments that has some fixed density of twist [12] and splay defects [12,13] [Fig. 1(a)]. If all the filaments are perfectly aligned, then they form a close-packed, hexgonal crystal, but in the process of aggregation, twist defects can form, when two filaments attach to the growing bundle with different relative orientations along their lengths [Fig. 1(a)]. Splay, or interrupted filament [13], defects arise when the filaments of different lengths adsorb and overlap. Different patterns of disorder will be shown below to lead to the selection of different quasi-equilibrium finite radii distributions. We call this a quasi-equilibrium since the defects in the bundle can be annealed away *in principle*, but this is highly unlikely for long filaments and strong cross linking, and the defects are therefore dynamically arrested in a metastable configuration. Long filaments have a high probability of having several twist defects along their length [5], and therefore get entangled and knotted [22] [Fig. 1(a)]. There is recent experimental evidence that in-vitro actin bundles do indeed have such twist defects [5], and that the sliding mobility of filaments within the bundle is negligible [5]. We wish to consider the implication of such quenched, i.e. static and random, defects for the width distribution of biopolymer bundles. A similar analysis for toroi-

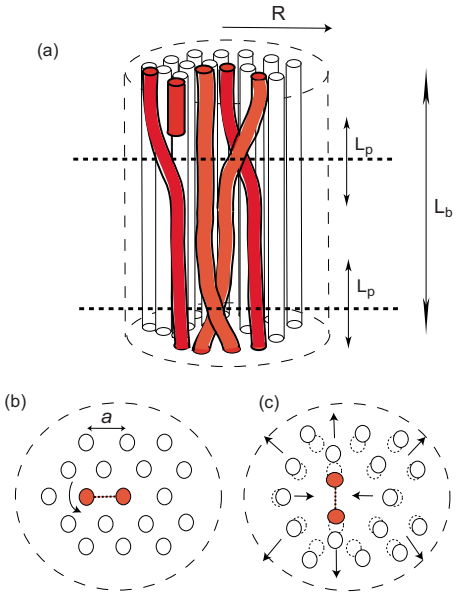

FIG. 1. (Color online) (a) Schematic picture of packing defects (red) inside a bundle of radius R and overall length L_b. The defect bends the filaments over a length L_p, with curvature of $\sim a/L_p^2$ [14]. Several twist defects and a single splay defect are shown. Twist defects along the length of the bundle can cause the filaments to form a knot. Far below or above the defect plane (horizontal dashed lines), the filaments are arranged in a two-dimensional hexagonal array (b). (c) In the defect plane there is a strain field in the surrounding filaments. Here we show how a twist defect (red) creates a strain field around it (arrows), by pushing the surrounding filaments from their perfectly hexagonal array (dashed circles).

dal packing of long, coiled filaments (DNA) was also shown to give rise to an optimum size selection [14].

To summarize, we will use below an equilibrium theory to determine the bundle size, while assuming that the defects inside the bundles cannot be annealed away. This assumption may be valid, for the following reason: while the bundle can explore the free energy landscape with respect to its "size" by adding filaments reversibly (since the binding energy per unit length is a few k_BT), annealing a defect out of the bundle requires large-scale rearrangement of many filaments, which has a very high energetic cost, and is therefore a very slow process.

First let us consider the aggregation of perfectly straight filaments, without any defects. When actin filaments attract each other due to some adhesion agent, they aggregate laterally. We will consider here the case of strong cross linking and long filaments, so that the interaction term dominates over the entropy term in the free energy, which we will neglect from now on [7]. The adhesion energy gain is driving the aggregation, and since the filaments on the surface have less adhesion energy (less neighbors), there is an energetic drive to increase the bundle thickness. Since we are working in the canonical ensemble with a fixed number of filaments in the solution, minimizing the total energy of the system is equivalent to minimizing the energy per filament. The adhesion energy per unit length per filament can be simply written as the energy of the entire bundle, divided by the number of filaments in a bundle [15]

$$E_{bind} \approx \frac{-\pi(R/a)\varepsilon_b[(R/a)-2]}{(R/a)^2}, \tag{1}$$

where ε_b is the adhesion energy per unit length, and $a \sim 10$ nm is the radius of the individual filaments and surrounding cross linkers [5,6]. The first term represents the bulk adhesion energy (negative) and the second term represents the surface energy (positive). This energy functional uniformly decreases for increasing radius, signaling that the bundle grows to infinite width, to maximize (minimize) the adhesion (overall) energy [Eq. (1)]. The observed widths of actin bundles seem to be constrained [5,6], and despite the mobility of the bundles, side-by-side annealing and further lateral aggregation of bundles does not occur, while the bundles do grow longer by longitudinal aggregation [5]. This observation is therefore at odds with the equilibrium theory described by Eq. (1), and is our motivation for looking at the effect of packing defects.

Consider now packing defects, where each defect involves an increase in the local energy due to several terms (Fig. 1): (i) Loss of adhesion energy due to broken cross-linking bonds at the site of the twist, (ii) the elastic energy of the bending and twisting the two actin filaments, (iii) the elastic energy of the deformed hexagonal lattice of filaments around the defect [Figs. 1(b) and 1(c) demonstrates this for the twist defects]. These energy terms apply to all types of defects. The first two energies are local inside the bundle cross section and can be summed into the core energy of the defect. This core energy E_c, includes therefore the broken cross-linker bonds and bending (twist) of the two actin filaments, which are spread over a healing distance L_p [Fig. 1(a)] [14]. The bundle is considered as infinitely long, and the defects are uniformly spread along its length, so that we can treat the defects as point defects in a two-dimensional circular cross section. The exact strain field for a distribution of defects inside a finite bundle is a complex problem. We wish here to present a simplified and general analysis, where we examine the effects of some extreme cases; (i) highly localized strain field $u(r)$ (where r is the radial coordinate from the defect center), where the overall strain energy is finite in the limit of large r, or (ii) a long-range strain field where the strain energy diverges in the limit of $r \to \infty$. For clarity we will describe below the effects of these two cases separately, while the real defects may have both properties.

Within the continuum description, the strain field in the surrounding bundle due to a localized defect depends on the nature of the defect, i.e. splay or twist defect; (i) an isolated *splay* will induce a strain field that decays as $u \sim 1/r$ [13] away from the defect core. Such a strain field will be referred to as a "monopole" force defect, and arises from any local dilation in the lattice. This is a long-range strain field in the sense that the total strain energy around such a defect diverges logarithmicaly with $r \to \infty$, in a two-dimensional lattice. (ii) A twist defect does not induce a finite Burgers vector, as the number of filaments enclosed by any loop that contains the defect axis is constant. The strain field in this case can be represented by a quadropole force center acting at the defect core [Fig. 1(c)]. The strain field from such a quadropole force center decays as $u \sim 1/r^4$ [16]. The twist defect may therefore also induce a local dilation (monopole), due to anharmonic interaction among the filaments [17], which results in a strain field of the form $u \sim 1/r$ [16]. Note that in two dimensions, except for the monopole field, all higher order multipoles give rise to a finite strain energy.

Inside a long bundle, where $L_b \gg L_p$, energy contribution from a single defect is negligible compared to the other terms in Eq. (1), the equilibrium stays at an infinite width and we are therefore led to consider a distribution of many defects. We will show below that a distribution of a field of defects can introduce an energy cost that grows for thicker bundles, and eventually balances the adhesion energy [Eq. (1)]. Let us first treat the case of a highly localized strain field, such as for the quadropole (and dipole) component, where the strain energy is independent of R for $R \gg a$. A uniform distribution of such defects, of cross-sectional density $\rho = 1/L^2$, will simply add $E_{defect} = \rho \pi a^2 E_c$ to the energy of Eq. (1), and the energy per filament is still minimal for an infinitely wide bundle.

Next let us consider what happens if close to the surface of the bundle the core energy of these defects E_c is lower than deeper inside the bundle. This may arise from the lower number of broken cross linkers for misplaced filaments at the surface, and the lower strain energy due to the small number of filaments displaced at the surface. Alternatively, the defects may not be strongly trapped close to the bundle surface, and can anneal away. Such a process may occur due to a finite mobility of the filaments on the bundle surface, which leads to effective "surface melting" of the outer layers of filaments, thereby annealing any defects. Both scenarios can be described by an outer layer of the bundle, of thickness λ [Fig. 2(a)], that does not contribute any defect energy (for

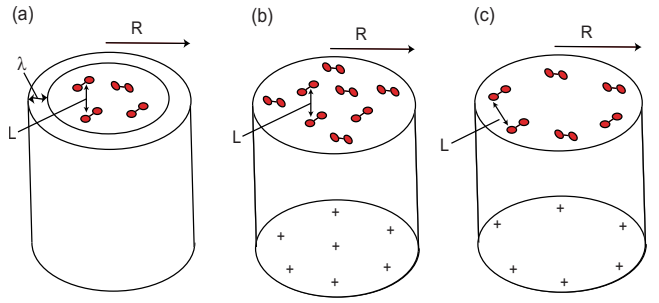

FIG. 2. (Color online) (a) Schematic picture of the empty-shell model; uniform population of defects (red pairs) at areal density $\rho = 1/L^2$ and core energy per unit length E_c, with an defect-free outer shell of thickness λ. (b) Schematic calculation of the uniform field of defects with long-range logarithmic elastic interactions in the bundle cross section, with a uniform cross section distribution of density ρ. This is treated as a uniform distribution of charges with logarithmic repulsion. (c) Same as in (b) for defects distributed only on the bundle surface.

simplicity). The overall energy of the defects (per unit length and per filament) in such a bundle is therefore given by

$$E_{defect} \approx \rho\pi(R-\lambda)^2 E_c/(R/a)^2. \tag{2}$$

The total energy per unit length per filament is now $E_{total} = E_{bind} + E_{defect}$ [Eqs. (1) and (2)]. We now find that for $E_c^* < E_c$, where $E_c^* = \varepsilon_b/(\rho a \lambda)$, the system has an minimum energy configuration of finite width [18], given by

$$R_{0,shell} = \frac{\lambda}{1 - E_c^*/E_c}. \tag{3}$$

As the defect core energy increases above its critical value E_c^*, the bundle radius shrinks, for a fixed density; more energetic defects result in thinner bundles. In the limit of $E_c/E_c^* \gg 1$, we find that the equilibrium radius approaches the thickness of the defect-free outer layer $R_{0,shell} \to \lambda$, while in the limit of $E_c \to E_c^*$ the equilibrium radius diverges. Above E_c^*, the system is dominated by the energy of the defects, while below this value the binding energy dominates. Our "empty-shell" model is an approximation, and the defect energy may change continuously as a function of the distance from the bundle outer surface. For defects without long-range strain fields, this approximation should be adequate. The equilibrium radius $R_{0,shell}$ decreases with increasing defect density ρ; behaving as $1/\rho$ for $E_c \to E_c^*$, and for large ρ approaches the value of λ. We therefore find that the localized defects, that are confined to the inner part of the bundle, drive the filaments to have a lower energy at the bundle surface, leading to a finite bundle radius. This form of "frustrated interactions" among the filaments is somewhat similar to the concept proposed by Henle *et al.* [7] for electrostatic interactions.

We now return to the problem of a uniform distribution of defects with a long-range strain field. In the limit of $L_p \gg R$ we can treat the strain field associated with the displacements of the filaments from the perfect hexagonal lattice, as purely two dimensional in the cross section of the bundle. For strain of the form $u \sim 1/r$, the defects can be treated as a two dimensional gas of charges, interacting via logarithmic repulsion [19] [Figs. 2(b) and 2(c)]. Note that since all defects induce the same strain field, they all have the same sign and repel each other. The problem therefore resembles a two-dimensional version of the famous Rayleigh instability of charged droplets [20]. In our case, the defects behave as elastic charges and their mutual repulsion breaks the infinitely thick bundle into bundles of finite radius. The interaction energy per filament due to a distribution of monopole defects, per unit length, is given by

$$E_{defects,b} \approx 2\pi k_b' \frac{1}{(R/a)^2} R^4 \rho^2 \ln(R/a), \tag{4}$$

$$E_{defects,s} \approx 2\pi k_s' \frac{1}{(R/a)^2} R^2 \rho \ln(R/a), \tag{5}$$

depending on whether the defects are arranged uniformly throughout the bulk of the bundle cross section, or are confined to the outer surface, and $k_{b,s}'$ combines the effective elastic stiffness of the filaments inside the bundle and various geometric factors. In both arrangements this energy will dominate at large R over the binding energy [Eq. (1)]. We therefore have a situation now where the bundles always have a finite equilibrium radius.

When a bundle is incompressible, and tightly packed, then each defect bends all the other filaments in the bundle cross section by the same amount, with curvature $\sim a/L_p^2$. This case was treated in [14] for toroidal packing. For a linear bundle with a uniform distribution of defects throughout the cross section, we can derive the defect energy along similar lines [14] [Fig. 1(a)]; divide the bundle of length L to slices of length L_p, within each there are $\rho_v L_p \pi R^2$ defects ($\rho_v = \rho/L_p$ is the volumetric density of defects). We assume that each filament passing inside such a slice develops a curvature of $\sim a/L_p$ due to each of the defects inside the slice. Since there are $(R/a)^2$ filaments in the bundle cross section, we finally get that the defects' energy per unit length per filament becomes

$$E_{defects,b} \approx K\rho_v L_p (a/L_p^2)^2 R^2 L_p \simeq K\rho \frac{(R/L_p)^4}{(R/a)^2}, \tag{6}$$

where K is the bending modulus of the filaments (energy per unit length).

The total energy per unit length per filament is now $E_{total} = E_{bind} + E_{defects}$, and has a global minimum at a finite equilibrium radius. Using Eqs. (4)–(6), respectively, and assuming $E_c < E_c^*$, we find that this radius is given by

$$R_{0,b}/a = \left(\frac{3}{2\alpha_b (a^2\rho)^2 \mathrm{W}[3e^{3/2}/(2\alpha_b (a^2\rho)^2)]} \right)^{1/3}, \tag{7}$$

$$R_{0,s}/a = \frac{1}{a^2 \rho \alpha_s}, \tag{8}$$

$$R'_{0,b}/a = \left(\frac{\pi(L_p/a)^4}{\alpha'\rho}\right)^{1/3}, \tag{9}$$

where $\alpha_{b,s} \equiv k'_{b,s}/\varepsilon_b$, $\alpha' \equiv K/\varepsilon_b$ and W is the Lambert-W function (or the Mathematica defined function ProductLog). We find that all the equilibrium radii $R_{0,b}, R_{0,s}, R'_{0,b}$ decrease with increasing defect density, while the radii also decreases with increasing the stiffness of the bundle (given by the different α's).

It was recently observed that the average thickness of the bundles increases with the concentration of adhesion agent [2,3,6], which within our model may modify the density of defects ρ and/or the ratio $\alpha, \alpha', \varepsilon_b/E_c$ between the binding energy and defect elastic energy. We find that in the limit of weak binding $R_{0,shell}, R_{0,b}, R_{0,s} \propto \varepsilon_b$, while $R'_{0,b} \propto \varepsilon_b^{1/3}$. The expected relation between the average binding energy and the concentration of cross-linking c agent at thermodynamic equilibrium is $\varepsilon_b \propto c\exp(\epsilon)/[1+c\exp(\epsilon)]$, where ϵ is the free energy of cross-linker-actin binding. At low concentrations and low binding energy ϵ, we therefore predict that the radius should increase either linearly or as the third root of the concentration. A linear relation was measured for depletion forces [2], while a weaker dependence was measured for protein cross linkers [3], presumably due to the larger value of the binding energy ϵ.

Alternatively, another possibility is that as the concentration of adhesion agent increases, the density of defects may decrease, leading to an increase in the average radius of the bundles. If the adhesion energy is large it could lead to fast mechanical annealing of twists when filaments join the bundle at the surface, and therefore reduce the density of such defects that are stuck in the bundle as it is forming. On the other hand, weak adhesion may allow thermal fluctuations to play a role in producing twists when filaments adsorb at the bundle surface, leading to an increased density of such defects; weakly bound bundles may aggregate in a "messier" fashion, resulting in more defects.

Note that there is a key issue of the time scales of the phenomenon we are dealing with. The energy functionals that we calculate allow us to estimate the forces that act on a filament when it is added to a bundle, i.e. as the bundle radius is growing. If during this growth process the annealing of defects is extremely slow, then the defects can be treated as frozen over the time scale that it takes the bundle to grow to its "equilibrium" radius [Eqs. (3), (7), and (9)], as calculated by our models. As long as the bundle radius is smaller then the calculated "equilibrium" radius, the effective force between a filament and the bundle is attractive, and a filament will tend on average to stick to the bundle and so the radius grows. As the radius passes the "equilibrium" radius, there is an effective repulsion due to the increase in the energy per filament, and this should hinder further growth. The repulsion is caused by the defects' contribution to the energy; for the long-range strain-field defects this repulsion is simply due to the elastic interaction energy. The sticking of a long filament to an existing bundle in a way which is defect free is highly unlikely, and the annealing of the defects can be a very slow process; removing a defect involves large scale motion along the whole length of the filaments (Fig. 1). If the system can evolve over a very long time, then it should eventually approach the annealed limit of no defects and a single bundle of largest radius.

The process of bundle aggregation from the solution is a dynamic process, best described in terms of growth equations. The total filament flux at the surface of a bundle of radius R (per unit length) is given by

$$\dot{N} = \frac{2R}{a^2}\dot{R} = 2\pi R a \rho_{ac}\frac{1}{\gamma}\left(-\frac{\partial E_{total}}{\partial R}\right) \Rightarrow \dot{R} = \beta\left(-\frac{\partial E_{total}}{\partial R}\right), \tag{10}$$

where ρ_{ac} is the concentration of filaments and γ is some effective friction coefficient (entropy is neglected). In addition to this drift in the bundle radius there is stochastic component due to fluctuations in the local concentrations of the filaments and binding agents. The probability distribution function $P(R)$ can then be derived from a standard Fokker-Planck equation of the form

$$\frac{\partial P}{\partial t} = \frac{1}{2}D_R\frac{\partial^2 P}{\partial R^2} + \frac{\partial(\dot{R}P)}{\partial R}, \tag{11}$$

where D_R is the diffusion coefficient in R space due to the different noise terms. The calculation is appropriate for a system with an infinite reservoir of actin filaments and cross-linking proteins, but does not qualitatively change in a closed system. The steady-state solutions of this equation using the energy functionals for the different models presented above, are all of the form: $P(R) \propto \exp[-2\beta(E_{total}(R) - E_0)/D_R]$, where E_0 is determined by the normalization requirement. For the empty-shell [Eq. (2)] we get a very shallow decay of the distribution for $R > R_{0,shell}$, of the form: $P(R) \propto \exp(-1/a - 1/R)$. For the surface monopoles [Eq. (5)], $P(R)$ decays as a power-law for large R, in the form: $P(R) \propto R^{-2\pi a^2 \rho\beta k/D_R}$. For the bulk distribution of monopoles [Eqs. (4) and (6)] we find a Gaussian decay, $P(R) \propto \exp(-R^2)$ for large R. Recently, the width distribution of actin filaments was measured [6], and found to behave as a Guassian with a well-defined peak. Such a distribution can be well fitted with the $P(R)$ we calculate using the bulk distribution of monopoles models [Eqs. (4) and (6)].

In a living cell the actin filaments form bundles in a variety of forms. Specifically, in the core of stereocilia the filaments seem to be in a perfectly regular, hexagonal lattice [21]. These bundles do not form by the lateral aggregation of pre-existing filaments; all the filaments in such a bundle polymerize together and elongate in synchrony from the stereocilia tip, where the polymerization of the filaments is promoted by tip-complex proteins. If the relative locations of the nucleation sites within this tip complex are maintained in a solidlike static structure, then the filaments which elongate from these nucleation sites will form a perfectly packed bundle. The width of these bundles is therefore not controlled by defect formation, and indeed can contain thousands of actin filaments [21], much thicker than the in-vitro bundles [2,3,6].

We conclude that random packing defects in bundles of long filaments, can lead to an effective pressure that limits the growth of the radius of such bundles. The rudimentary treatment given here should be improved in the future by a treatment of the full three-dimensional problem [13,22,23] of the complex strain fields of a population of twist defects inside a bundle that is also free to twist and bend as a whole. Recent high-resolution images of actin bundles obtained using transmission electron microtomography and atomic force microscopy [24] provide first indications for the existence of defects in the actin packing. Future experiments may provide tests of our model by mapping the distribution of defects and its dependence on the conditions of the bundling process.

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