Stretching globular polymers. I. Single chains

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(Received 15 December 2004; accepted 4 March 2005; published online 13 May 2005)

We review the force-extension behavior of polymers collapsed in poor solvent, modified to include the effects of semiflexibility and considered for globules with "ordered" and "disordered" internal structures. A series of ordered globules is used as a model for the unbinding of a disordered globule beneath its glass transition and for multiple-repeat proteins such as the poly-Ig-domain titin used in atomic force microscopy studies. These single-chain results form the foundation for the treatment of cross-linked networks of globular polymers. © 2005 American Institute of Physics. [DOI: 10.1063/1.1898213]

I. INTRODUCTION

The quasistatic force-extension behavior of polymer chains is one of the best-explored branches of polymer theory. Beginning with the Langevin-function force-extension response of random-walk chains,¹ theorists have gone on to provide models for the force-extension behavior of semiflexible chains,^{2,3} α helices,⁴⁻⁶ plectonemes in twist-storing polymers,⁷ and copolymers.⁸

Further studies of the force-extension response of free chains have paralleled the study of the collapsed state of polymers in poor solvent. Following the mean-field treatment of flexible polymers in good and poor solvents9 of Flory and the Green's function description of similar systems¹⁰ of Lifshitz, a number of scaling and mean-field arguments have been developed with regard to the structure, stability, and formation of polymer globules.¹¹ The most extensive attention has been given to the "Gaussian globule" of a collapsed chain that is densely packed, but still uncorrelated in its direction. These globules have been studied, and the mechanical response of individual globules examined under extension¹² and various regimes of compression.¹³ More recently, experimental observations of DNA in poor solvent^{14–16} and an improved theoretical understanding of semiflexible polymers^{3,17,18} have given rise to theories of globules with a well-defined internal structure. The development of these theories have also been encouraged by the strong analogy between heteropolymers and proteins.¹⁹

In recent years, experimental work has developed tools for the micromechanical manipulation of polymer strands, particularly optical tweezers^{20–23} and atomic force microscopy,²⁴ that have made it possible to probe the mechanical response of single polymer chains and globules directly. Results from these experimental studies have largely supported the existing theoretical results for stretching free, single chains, and extended general polymeric properties such as persistence length and mechanical stability to biopolymers.

In this paper, we review existing theoretical models for the force-extension behavior of single collapsed chains, with crude effects of internal structure of globules with a native conformation, or without a native conformation but beneath the glass transition. In Sec. II, we briefly discuss the classical model of semiflexible polymers used for all subsequent results. Sections III A and III B furnish descriptions of globules with and without specific native conformations, which we refer to as "ordered" and "disordered" globules, respectively. For disordered globules, we review the existing theory for the force-extension behavior of spherical and toroidal globules, and modify its predictions to account for the effect of semiflexibility in the extended chain. We also incorporate the idea of globule "bursting" predicted to occur in spherical globules into the treatment of toroidal globules. In Sec. III B we develop a simple, versatile model of ordered globules, and connect this model to experimental data on protein stretching and simulation data for spherical disordered globules stretched beneath their glass transition, effectively linking the ordered and disordered models.

novel adjustments to account for semiflexibility and the

II. SEMIFLEXIBLE CHAINS

Before treating the globules themselves, we first must describe the unbound, semiflexible state of the polymer chain. A substantial literature now exists on semiflexible (or "wormlike") chains. These are simply polymer chains with an intrinsic bending energy characterized by a persistence length l_p , which represents the distance over which the direction of the chain becomes uncorrelated.²⁵ Clear physical instances of semiflexible chains include single-molecule DNA, long carbon nanotubes, α -helical polypeptides, Aramid/ polyphenyleneterephtalamide, and Zylon/polybenzoxaloe, among others. It is worth noting that biopolymers appear particularly suited for treatment as semiflexible chains as a result of their relatively wide, complex polymer backbones. For the purposes of this paper, we will describe semiflexible chains by the mean-field Hamiltonian by Ha and Thirumalai.18

0021-9606/2005/122(19)/194901/6/\$22.50

122, 194901-1

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194901-2 A. Craig and E. M. Terentjev

$$\beta \mathcal{H} = \int_0^L ds \frac{l_p}{2} \left(\frac{d\mathbf{u}}{ds}\right)^2 + \psi(\mathbf{u}^2 - 1), \qquad (1$$

where $\mathbf{u}(s)$ is the tangent vector of the chain, *s* is the contour length along the chain, $\beta = (kT)^{-1}$, and ψ is a Lagrange multiplier that enforces the global average constraint $\langle \mathbf{u}^2 \rangle = 1$. For $L \gg l_p$, semiflexible chains follow the force-extension curve given by

$$\beta f(x) = \frac{3x}{4Ll_p(1 - x^2/L^2)^2},$$
(2)

where f and x are the force and imposed end-to-end extension, respectively.^{3,17} The force-extension behavior of Eq. (2) can be seen up to $L \sim l_p$ in both the mean-field treatment of semiflexible chains and numerical solutions of the exact Kratky–Porod model.²⁶ For the regime of chain lengths and persistence lengths discussed here, theory suggests that the discrete nature of the chain only becomes important at deformations $x/L > 0.95 \cdot 0.99$ (Ref. 27) and yields a forceextension relation of the form $\beta f(x) \propto (1-x/L)^{-1}$ that effectively makes the chain stiffer than Eq. (2) predicts. This observation keeps with earlier experimental atomic force microscopy (AFM) force-extension spectra for dextran²⁸ that are dominated by monomer-specific effects in this regime. However, we will neglect discrete-chain effects, as they do not dramatically affect the globule bursting key to this paper. Instead, we use Eq. (2) as the simplest result which improves on the classical Langevin force-extension relation²⁹ by incorporating semiflexibility. Equation (2) also has the advantage of its simple and tractable associated free energy

$$\beta F_{\rm sf}(x) = \frac{3L^3}{8l_p} \frac{1}{L^2 - x^2},\tag{3}$$

which we also use throughout this paper for the stretching energy of "free chain" segments found in globules under extension.

III. MODELS OF POLYMER GLOBULES

A. Disordered globules

We use the term "disordered" (or random) globules to refer to collapsed polymer states analogous to the Gaussian globules formed when flexible polymers collapse, but generalized to semiflexible chains. These globules are predicted to be either spherical (for long chain lengths or extremely poor solvent) or toroidal (for long persistence lengths).³⁰ Regardless of their undeformed shape, when extended these globules are thought to be described by a "ball and chain" model,¹² in which the globule remains basically intact, but releases some of the polymer as a free chain (Fig. 1).

1. Spherical globules

If we model the polymer-solvent interaction with a simple surface-tension term, the free energy of this ball-andchain system can be written for a spherical globule as



FIG. 1. Spherical disordered globule with total length \mathcal{L} and unbound fraction κ under extension.

$$F(\kappa, x) = F_{\rm sf}(\kappa, x) + F_{\sigma}(\kappa, x), \tag{4}$$

where κ denotes the fraction of the total length in the tether. If we have a monomer size b^2 and a free-energy cost γ per unit surface area exposed to the solvent, we can rewrite our units in dimensionless form: $\mathcal{F}=\beta F$, $\tilde{f}=\beta fb$, $\mathcal{L}=L/b$, ϕ $=l_p/b$, $\Gamma=\gamma b^2$, and $\chi=x/b$. We use these dimensionless units henceforth. For a globule with radius of gyration \mathcal{R}_{glob} given by $\mathcal{R}_{glob}=[(3/4\pi)\mathcal{L}(1-\kappa)]^{1/3}$, we can now write the semiflexible contribution to Eq. (4) from the tether as

$$\mathcal{F}_{\rm sf}(\kappa,\chi) = \frac{(\mathcal{L}\kappa)^3}{8\phi} \frac{1}{(\mathcal{L}\kappa)^2 - (\chi - \mathcal{R}_{\rm glob})^2}.$$
 (5)

The surface-area contribution follows as

$$\mathcal{F}_{\sigma}(\kappa,\chi) = \Gamma \mathcal{L}\kappa\pi + \Gamma (36\pi(\mathcal{L}(1-\kappa))^2)^{1/3}, \tag{6}$$

where the first term is the surface energy of the solventexposed tether, and the second that of the remaining globular surface. Here we have assumed that the polymer chain has a roughly cylindrical form with diameter *b*; realistic, noncylindrical polymers will have slightly different numerical prefactors in \mathcal{F}_{σ} from Eq. (6), but the energy should scale identically in the key parameters \mathcal{L} and κ . We have also neglected the effects of the bending energy required to form the globule, but we can imagine that the number of turns (and so as the bending energy) scales with the surface area of the globule and would so only add another numerical prefactor to the globule term in Eq. (6).

The total free energy can now be found by minimizing Eq. (4) with respect to κ . As detailed in previous studies, ^{30,31} the fraction of free chain κ can suddenly jump to unity as we extend beyond a critical value χ_c . For $\Gamma \simeq O(1)$, this (dimensionless) critical extension is $\chi_c \approx \mathcal{L}\Gamma \sqrt{2/3}$. The jump in κ marks a discontinuous first-order transition that corresponds to the bursting of the globule, and comes about when the surface free energy gained by keeping the polymer stored in the spherical globule and partially out of the poor solvent is outweighed by the stretching free energy to be gained from releasing the entire polymer length as a free chain. The appropriate force-extension curves follow from $\overline{f} = -\partial_{\gamma} \mathcal{F}(\kappa, \chi)$, which we obtain for a range of "strains" $1 \le x/\mathcal{R}_{glob}$ $\le \mathcal{L}/\mathcal{R}_{glob}$. Note that since $\mathcal{L}/\mathcal{R}_{glob} \sim \mathcal{L}^{2/3}$, we obtain maximum strains on the order of 10^2 for $\mathcal{L}=1000$, a high value that will recur throughout this paper and figure importantly into the behavior of networked globules. We plot f against χ/\mathcal{R}_{glob} in Fig. 2 for varying scaled persistence length ϕ , and in Fig. 3 with a varying effect of poor solvent Γ .

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FIG. 2. Force-extension curve of a disordered globule with varying chain stiffness ϕ (values indicated on plot) for surface tension $\Gamma=1$ and length $\mathcal{L}=1000$. The dashed line indicates the size $x=R_{\text{glob}}$, which is the initial chain size, the cutoff of numerical calculation.

Though the graphs closely resemble those from Ref. 30, there is a small difference in the near-zero initial force, which represents an error in the numerical derivative $-d\mathcal{F}/d\chi$ at $\chi \approx 1$. More importantly, we have made the improvement of explicitly incorporating semiflexibility into the chain response. In particular, Fig. 3 indicates that increasing the persistence length $l_p = b\phi$ decreases the force required to stretch a globule, since more rigid chains contain few Kuhn lengths relative to more flexible ones and so act as weaker entropic springs. This trend will recur throughout our treatment of different polymer globules. The unbinding threshold χ_c also increases with persistence length, as one might expect if relatively less free energy can be gained from releasing the chain out of the globule. Though we will see that chains with $\phi \ge 10$ and $\mathcal{L} = 1000$ form toroids rather than spherical globules, Fig. 2 does illustrate the generic effects of increasing chain rigidity.

The simplified ball-and-chain model of the random globule produces force-extension curves that conflict with Monte Carlo studies of random globules.³² These suggest that the polymer winds off the globule in small sections due to con-



FIG. 3. Force-extension curve of a disordered globule with varying surface tension Γ (values indicated on plot) for chain stiffness $\phi=10$ and length $\mathcal{L}=1000$. The dashed line indicates the size $x=R_{\rm glob}$, which is the initial chain size, the cutoff of numerical calculation.



FIG. 4. Toroidal globule under extension.

formational restrictions on the monomer level within the globule. As temperatures rise these conformational restrictions ease, and one obtains the same smooth behavior as in the ball-and-chain model shown above. However, we also note that Ref. 30 qualitatively reproduces the smooth force-extension curve shown in Figs. 2 and 3 as an average of 100 Monte Carlo runs made below the glass transition. The simulated "stiff cantilever" force-extension curves of the Lennard-Jones globules in Ref. 32 also follow the plateau-and-rise shape of the ball-and-chain model, though conformational restrictions again result in a higher plateau force at T=0 than at other temperatures. We suggest approximating this effect by simply introducing a temperature-dependent resistance $\mu(T)$ into the ball-and-chain model such that $\Gamma_{\text{chain}} = \Gamma(1 + \mu(T))$.

2. Toroidal globules

Experimental work^{15,16} has shown that semiflexible polymers with large persistence lengths, such as DNA and actin, condense into a toroidal phase when placed into a poor solvent, an observation since incorporated into the body of polymer theory.^{14,33–35} The toroidal conformation is simply the result of having l_p so large relative to the surface contact energy Γ that even though the chains are in a collapsed conformation, they will not fold freely as in the Gaussian globule, but will prefer to minimize the local bending energy by stacking on top of each other in circular loops, with a roughly hexagonal packing of the coil. The energy balance between the packing and bending energies indicates that the major radius of a toroidal globule is given by³⁶

$$\mathcal{R}_{\rm tor} = \frac{R_{\rm tor}}{b} = \left(\frac{\mathcal{L}(1-\kappa)\phi^2}{2\pi^2\Gamma^2}\right)^{1/3}.$$
(7)

A simple scaling argument suggests that the toroidal globule is stable against collapse into a spherical globule when its major radius exceeds the minor radius $\varrho = r/b \sim (\mathcal{L}/(2\pi \mathcal{R}_{tor}))^{1/2}$, i.e.,

$$\mathcal{L} \le \frac{\phi^3}{\Gamma^3}.\tag{8}$$

Note that our estimate for globule stability differs significantly from that given in Ref. 14 due to differences in the scaling relations for the major radius. Under extension, these toroidal globules can be modeled with roughly the same form of free energy as spherical globules, Eq. (4), albeit with a suitably modified surface-energy term. Assuming that the tether pulls off the globule tangentially as shown in Fig. 4,

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FIG. 5. Force-extension curve of a toroidal globule with varying chain stiffness ϕ (values indicated on plot) for surface tension $\Gamma=1$ and length $\mathcal{L}=1000$. The dashed line indicates the size $x=R_{tor}$, which is the cutoff of numerical calculation.

we have the free energies

$$\mathcal{F}_{\rm sf}(\kappa,\chi) = \frac{(\mathcal{L}\kappa)^3}{8\phi} \frac{1}{(\mathcal{L}\kappa)^2 - (\chi - \mathcal{R}_{\rm tor})^2} \tag{9}$$

and

$$\mathcal{F}_{\sigma}(\kappa,\chi) = \frac{5\pi}{2} \Gamma \sqrt{2\mathcal{L}(1-\kappa)\mathcal{R}_{\text{tor}}} + \sqrt{2}\Gamma \mathcal{L}\kappa.$$
(10)

Note that \mathcal{F}_{σ} actually incorporates the bending energy for the formation of the globule; the bending energy associated with the torus is given by $\mathcal{F}_{\text{bend}} = \mathcal{L}(1-\kappa)\phi/(2\mathcal{R}^2)$, which simplifies to $(\pi/2)\Gamma\sqrt{2\mathcal{L}(1-\kappa)\mathcal{R}_{tor}}$ when we apply $\mathcal{R} = \mathcal{R}_{tor}$ from Eq. (7). This is in marked contrast to Eq. (4) for spherical globules, which does not explicitly account for the bending energy within the globule. As before, we minimize with respect to κ to obtain the actual free energy at imposed deformation χ . Again, we obtain a bursting of the globule at some χ_c , as can be seen in Fig. 5. This bursting is clearly implied by the fact that the surface area of the toroid scales as $\sim \phi^{1/5} L^{3/5}$, very close to the $\sim L^{2/3}$ scaling of the spherical globule. Thus, the balance between surface energy and tether tension should be similar in toroids to the same balance in spherical globules, and hence bursting should occur. Note that increasing the chain rigidity ϕ also increases \mathcal{R}_{tor} and so we reach full extension at lower values of the strain χ/\mathcal{R}_{tor} .

B. Ordered globules

In contrast to the gradual stretching of the toroidal and random globules with no internal structure, we now turn our attention to globules which release the stored length discontinuously when subjected to a critical force f_c . A physical example of this case would be a globule with a relatively strong bond, which we term the "lock," between two topologically distant parts of the chain and weak bonds elsewhere along the chain. Such a globule will resist unbinding until the lock has been overcome at force f_c , at which point it suddenly reverts to the coil state. Admittedly, strong, long-



FIG. 6. Ordered globule under extension. The shaded area marks the region with a bond between two topologically distant sections, the "lock."

ranged bonds could arise by chance in a small proportion of the disordered globules of Sec. III A. However, we use the term "ordered" globules since we require that long-ranged bonds occur in the whole ensemble of these globules, which essentially requires that the globules have a native structure. Proteins held together at distant points by disulfide bridges or strong hydrophobic interactions and RNA "clovers," are clear candidates for the ordered globule model. Highly cooperative structures (like many small proteins) can also be modelled as ordered globules in our sense, since applying f_c disrupts their cooperative pattern and results in the complete unbinding of the globule. Regardless of the details of the bonding, the essential features of ordered globules for our purposes are presented in Fig. 6. For proteins, the critical unfolding force is generally on the order of 100 pN. Note that our algorithm specifies not the absolute force f, but the dimensionless force \tilde{f} , the actual value of which depends on temperature T and chain width b. If we assume that b for a peptide is ~5 Å and $T \approx 300$ K, we arrive at a value of kT/b=8 pN. Under these conditions, a value of $\tilde{f}=2$ in Fig. 7 corresponds to an unbinding force of 16 pN, while $b \sim 2$ Å for a thinner chain would have $\tilde{f}=2$ represent 8 pN, and so on.

If we consider an ordered globule with a cutoff force \overline{f}_c , length \mathcal{L} , initial bound length \mathcal{L}_{bound} , and



FIG. 7. Force-extension curve of an ordered globule with $\phi=1$ for cutoff force $\tilde{f}_c=20$, bound length $\mathcal{L}_{bound}=500$, and length $\mathcal{L}=1000$. The dashed line indicates the force-extension curve of the pure semiflexible chain with $\phi=1$ and length $\mathcal{L}=1000$.



FIG. 8. Ordered globules in series.

$$\chi_c \approx \left(1 - \frac{2\sqrt{3}}{\sqrt{3 + 32\tilde{f}_c \phi}}\right) \mathcal{L}_{\text{bound}}$$
(11)

as the critical extension at which the force on the chain equals \tilde{f}_c in Eq. (2), the free energy of the ordered globule is just

$$\chi < \chi_c, \quad F(\tilde{\mathbf{f}}_c, x) = \frac{3(\mathcal{L} - \mathcal{L}_{\text{bound}})^3}{8\phi} \frac{1}{(\mathcal{L} - \mathcal{L}_{\text{bound}})^2 - \chi^2},$$

$$\chi > \chi_c, \quad F(\tilde{\mathbf{f}}_c, x) = \frac{3\mathcal{L}^3}{8\phi} \frac{1}{\mathcal{L}^2 - \chi^2}.$$
(12)

In effect, the ordered globule follows the force-extension curve for a semiflexible chain of length $(\mathcal{L}-\mathcal{L}_{bound})$ until reaching χ_c , at which point the chain follows the curve for a chain with the same ϕ and length \mathcal{L} . This is illustrated by the dashed line in Fig. 7, which represents the force-extension curve for pure semiflexible chain.

1. Ordered globules in series

The logical extension of a single ordered globule is a series of ordered globules, as one might obtain in a repeat polyprotein such as the titin strands used in atomic force microscopy experiments,^{21,37} or the "necklaces" of small globules (see Fig. 8) hypothesized to exist in unfolded random heteropolymers.^{8,38} If we assume that our series has *n* globules, each with bound length \mathcal{L}_i and bond strength \tilde{f}_c^i (with index *i* arranged in increasing order of the bond strength), the free energy follows as

$$F = \frac{(\mathcal{L} - \mathcal{L}_{j+1})^3}{8\phi} \frac{1}{(\mathcal{L} - \mathcal{L}_{j+1})^2 - \chi^2},$$
(13)

where the remaining bound length $\mathcal{L}_{j+1} = \sum_{i=j+1}^{n} \mathcal{L}$; the χ_c^i are those values of the extension where $-dF/d\chi = \tilde{f}_c^i$, and $\chi_c^j < \chi < \chi_c^{j+1}$.

The free energy of a series of ordered globules found in Eq. (13) is the free energy implicit in the piecewise fits of force-extension curves with semiflexible force-extension relations, as AFM experimenters have long used to assess the protein unfolding data.^{37,39–42} As such, we match the ordered-globule-series model against the force-extension measurements of the immunoglobulin domain of titin, reported in Ref. 37, in Fig. 9. An approximate fit can be found in a series of ordered globules with n=5, $l_p=1.6$ nm, and $f_c^i \approx 300$ pN $\forall i$. One finds a relatively poor fit to the first globule unbinding, though this may be a result of the initially noisy force data obtained for this small extension; the fits



FIG. 9. Ordered globules in series (circles) fit to experimental titin unfolding data (solid line), (Ref. 37) with n=5, $l_p=1.6$ nm, and $f_c^i \approx 300$ pN. We thank D.A. Smith for the data.

also suffer from the fact that the measured force-extension curve cannot drop instantaneously to lower values of the force after a globule unbinds, but slopes down gradually instead. One must also concede that as it is, this model is itself incomplete, as the exact values of the f_c^i must be predicted from molecular-dynamics simulations or the known properties of the bonds holding the protein together. However, the lack of detail in the ordered globule model lends it the advantage of being generalizable to all cooperative proteins that do not deform gradually under extension.

We also use the ordered-globule-series free energy as a model for the discontinuous unbinding of a random globule in the glassy phase, as alluded to in Sec. III A. Beginning with $\mathcal{L}_{bound} \sim \mathcal{L}$, that is, with nearly all the polymer length locked into the globules, we then averaged the forceextension curves over 50 members of an ensemble randomly distributed in \mathcal{L}_i and Gaussian-distributed in \tilde{f}_c^i with mean $\langle \tilde{f}_c^i \rangle$ and standard deviation ρ as shown in Fig. 10. Intriguingly, the resulting averaged curve qualitatively reproduces an averaged force-extension curve taken from explicit Monte Carlo simulations of a globular Lennard-Jones chain.³⁰ Aver-



FIG. 10. Force-extension curve of series of ordered globules with Gaussiandistributed cutoff force $\tilde{f}_c^i(\langle \tilde{f}_c^i \rangle = 3, \rho = 0.1)$ for random bound lengths \mathcal{L}_i , n=20.

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aging over the individual responses of the globules yields a curve that rises as the initial unbound length stretches out, reaching a force plateau like that of the disordered globule model, with a final rise where the last globule unbinds and the system stretches as a pure semiflexible chain.

We note that this crude model does not reproduce the discontinuity in the force-extension curve that corresponds to the unbinding of the disordered globule. Nevertheless, one can reproduce this dip if the \mathcal{L}_i are not distributed evenly across all length scales, but have some minimum length \mathcal{L}_{min} . In this case, each single globule (and so as the average) should have a minimum in its force-extension curve at χ $-\mathcal{L}=\mathcal{L}_{min}$, but the average force-extension curve will display a force plateau for χ - $\mathcal{L}=\mathcal{L}_{min}$, producing a discontinuity.

IV. CONCLUSION

Unfortunately, single-globule experiments have not yet assessed the stretching behavior of random globules, restricting our discussion to a theoretical level. Rather than dealing with homopolymer globules, AFM single-globule experiments have focused on protein unfolding,^{37,40} polymer adsorption in poor solvent,^{43,44} or the mechanical properties of α helices.⁴⁵ Empirical confirmation of the force-extension behavior of the disordered globules is a key piece of support needed to justify the conclusions of this paper.

In this context, we have provided a partial review of the literature on the force-extension response of globular polymer chains. We have modified existing models to include semiflexibility explicitly, and have distinguished between ordered and disordered globules as limiting cases of globules with and without internal structure. Further, we have shown how one may reproduce the force-extension results for disordered globules as an average over chains of ordered globules. Despite their differences, both classes of globules display force-extension curves which have discontinuities and remain well-bounded for fairly high extensions, two results which will be central to our discussion of networks of globules in the next paper.

ACKNOWLEDGMENTS

The authors thank Dr. Samuel Kutter, Samit Ahir, and Sir Sam Edwards for useful discussions and insights that went into the creation of this paper. We are particularly grateful to D. A. Smith and co-workers for the use of their AFM titin unbinding data. This research has been made possible by a grant from the Gates Cambridge Trust.

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