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## **Abstract**

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## **Comments**

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# Fragility and mechanosensing in a thermalized cytoskeleton model with forced protein unfolding

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We describe a model of cytoskeletal mechanics based on the force-induced conformational change of protein cross-links in a stressed polymer network. Slow deformation of simulated networks containing cross-links that undergo repeated, serial domain unfolding leads to an unusual state—with many cross-links accumulating near the critical force for further unfolding. This state is robust to thermalization and does not occur in similar protein unbinding based simulations. Moreover, we note that the unusual configuration of near-critical protein cross-links in the fragile state provides a physical mechanism for the chemical transduction of cell-level mechanical strain and extra-cellular matrix stiffness.

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The importance of mechanical cues for understanding cell behavior is increasingly recognized. Stem cell differentiation [1,2], tissue morphogenesis [3] as well as cell growth [4] and death [5] are known to be affected by cell shape or by the stiffness of the surrounding extra-cellular matrix. The molecular mechanisms by which such mechanical cues produce biochemical responses (termed mechanosensing) are only starting to be elucidated, but are often assumed to involve conformation changes in structural and signalling proteins [6–8]. Similarly, the anomalous mechanical response of cells is not understood despite the identification of the cytoskeleton’s major structural constituents and considerable modeling effort [9–11]. Rheological measurements on living cells find a rather unusual weak power-law scaling  $|G^*(\omega)| \sim \omega^\beta$  with a nonuniversal exponent  $0.1 < \beta < 0.25$  [12–17]. Similar unusual mechanical responses are found amongst soft glassy materials such as foams, emulsions, and pastes [12,18], which seem, at first glance, rather unlike cells. In contrast, purified actin does not exhibit such a response, having instead a frequency independent plateau at low frequencies [19,20]. Studies of actin networks containing the cross-link proteins filamin [21,22] or  $\alpha$ -actinin [23], however, have reproduced the weak power-law rheology as well as other aspects of the cell response, such as stress-induced stiffening.

These results suggest that understanding the dynamic processes associated with cross-linking molecules may be the key to understanding the origin of the cellular mechanical response, which in turn may be a prerequisite for understanding mechanosensing. Many cross-linking molecules have at least two properties that could cause network stress relaxation: force-induced unbinding from cytoskeletal filaments and serial unfolding of multiple internal protein domains that elongate the molecules. Recently, networks of actin filaments and serial unfolding cross-linking proteins have been investigated using athermal simulations [24,25]. Under deforma-

tion, these networks often self-organize into an unusual “fragile” state—a significant proportion of cross-links develop tensions slightly less than the critical tension for unfolding. It has been suggested [25] that the unusual stress relaxation spectrum due to cross-link unfolding in the fragile state may give rise to nonuniversal power-law rheology similar to that seen in cells. Indeed, the mathematical similarities between this problem and the soft glassy rheology (SGR) model [26] may allow this approach to explain the wealth of glasslike behavior recently observed in cells [27].

In this paper, we perform simulations of a cross-linked network simulations with a simplified network geometry to determine if the fragile state is stable under thermalization and whether a similar fragile state can be generated by forced unbinding rather than serial unfolding. First we turn off thermally activated processes to verify that our simplified geometry produces a fragile state akin to the earlier simulations [24,25]. When thermally activated unfolding is added, the fragile state robustly persists, with a small renormalization of the critical force. In contrast, comparable models with forced unbinding never accumulate near critical forces. While we find the slight renormalization of the critical force in the thermalized case is compatible with cell-like weak power-law rheology, cooperativity in our system precludes the direct calculation of network rheology. The unusual, near-critical arrangement of cross-links in the fragile state, however, is well suited to a mechanosensory function. We hypothesize that, by modulating the binding of signaling species, unfolding cross-link domains function as biochemical transducers of cytoskeletal deformation.

Both actinin [28] and filamin [29], as well as other cross-linking proteins, contain repeated domains (e.g., spectrin or Ig domains), that can be serially unfolded under an applied force, see Fig. 1(a). Both molecules also bind reversibly to actin filaments [30,31], unlike the irreversible biotin-avidin bonds used in some in vitro studies [20,32]. The mean unfolding or unbinding time for a molecule under tension is typically described by the Bell model [33]

$$\tau_B(F) = \tau_a \exp \left[ E_B \left( 1 - \frac{F}{F_c} \right) \right], \quad E_B = \frac{F_c r_o}{k_B T}, \quad (1)$$

where  $\tau_a$  is a molecular attempt time,  $F_c$  is a critical force,  $r_o$  is a characteristic bond length scale, and  $k_B T$  is the thermal

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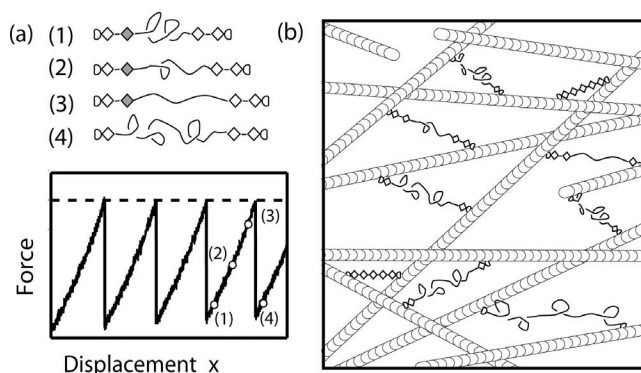


FIG. 1. Schematic representation of serial unfolding and the cytoskeleton. (a) As cross-links are extended, domains serially unfold with typical force vs. extension curves having abrupt transitions at a critical force  $F_c$ , corresponding states are labeled. (b) Our model of the cytoskeleton consisting of a network of generic semiflexible polymers and partially unfolded, extensible cross-links.

energy. The exponential form causes small changes in tension to yield rather large changes in unfolding time. As domains serially unfold, the molecule becomes progressively longer and longer. The entropic elasticity of the unfolded protein causes a springlike response between unfolding events, producing a “sawtooth” force-extension profile, Fig. 1(a).

We hypothesize that some cross-links unfold or unbind under physiological stresses [unfolding is sketched in Fig. 1(b)] and that the resulting self-organized fragile state may enable high-sensitivity sensing of cytoskeletal deformation. Simple estimates suggest that intracellular stresses are sufficient to lead to domain unfolding. Estimates of cellular traction forces range from 100–1000 Pa [34]. A stress of 100 Pa equals 100 pN/ $\mu\text{m}^2$ . In a gel of short filaments with  $\sim 30$  cross-links/ $\mu\text{m}^3$ , tension would be carried through  $\sim 10$  (or  $30^{2/3}$ ) cross-links/ $\mu\text{m}^2$ . The resulting 10–100 pN forces are sufficient to unfold spectrin [28] and Ig [29] domains, respectively.

For our simulations, we construct two-dimensional networks having periodic connectivity in the left or right direction, whose nodes are initially offset from a triangular lattice by a Gaussian-distributed amount, Figs. 2(a) and 2(b). Force carrying mechanical links connect these nodes (15% of the nearest-neighbor bonds are left empty to introduce topological disorder). Networks larger than roughly 25 by 35 nodes ( $\sim 10^4$  links) give results that are essentially independent of system size and changes in network disorder. To model serial unfolding, each link has a linear “sawtooth” force-extension curve  $F = k[(x - x_0) \bmod x_c]$ , where  $k$  is a spring constant,  $x$  is the instantaneous link extension,  $x_c \equiv F_c/k$  is the critical extension for bond rupture, and  $x_0$  is the link length at the beginning of the simulation (typically 5–100  $x_c$ ). Unlike the cytoskeleton and previous more realistic simulations [24], our network does not contain separate rodlike and cross-link elements. Each of the simulated links may be considered conceptually equivalent to a single inextensible rod of length  $x_0$  connected in series with a cross-link having an infinite number of unfoldable domains. Compressed links generate a compressive force (for  $x < x_0$ ,  $F = -k[(x_0 - x) \bmod x_c]$ ).

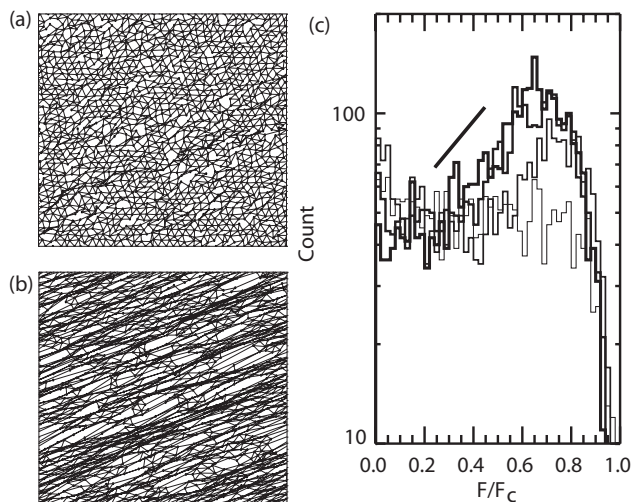


FIG. 2. Representations of our simplified model network and its force distribution without activated unfolding. (a) and (b) the network at strain  $\gamma=0.3$  and 1.5, respectively. (c) Probability distributions of scaled force, curves for strains  $\gamma=0.3, 1.0, 1.5$ , and 2.0 (thin to thick), respectively. Line represents exponential behavior.

The network is sheared by translating the nodes clamped to the upper boundary in a series of small steps ( $\Delta\gamma < 10^{-3}$ ) at a constant strain rate  $\dot{\gamma}(t) = \dot{\gamma}t$ . All nodes are first displaced according to an affine shear deformation, and then relaxed to mechanical equilibrium (zero total force on each node) by moving the nonboundary nodes using an overdamped steepest descent algorithm. During relaxation, links move freely between branches of the force extension curve until an equilibrium configuration is reached. This is equivalent to assuming that domains instantaneously unfold when the tension reaches  $F_c$  and refold at zero tension.

To model Bell-type thermally activated processes a kinetic Monte Carlo (KMC) algorithm is used. The expected unfolding rate of each tensed ( $F > 0$ ) link is computed from its tension and the Bell model [rate =  $1/\tau_B(F)$ ]. Consistent with the KMC algorithm, an exponentially distributed time step is generated which is inversely proportional to the total unfolding rate, and the link to unfold is selected in a rate weighted manner. If the total rate is too low, additional shear steps are inserted to avoid correspondingly large time/strain steps. To model the thermally activated unfolding of the selected subcritical link, its force extension curve is temporarily modified to be zero in the  $x_c$ -wide extension interval it occupies. The network is then relaxed, with the selected link typically moving into an adjacent, nonzero interval, with neighboring links often undergoing instantaneous (critical) unfolding or refolding. In rare instances when the link remains in the zeroed interval, the force-extension curve is returned to normal and the network re-relaxed.

In a separate study where network relaxation proceeds by force-accelerated unbinding, rather than unfolding, we used precisely the same algorithm to model both instantaneous (critical) and Bell-type (subcritical) unbinding, but employed a modified force extension curve. The unbinding force-extension curves had a single sawtooth period [ $F = k(x - x_0)$  for  $|F| < F_c$ , = 0 otherwise]. As before activated unbinding

entails the KMC selected link first having its force set to zero, followed by network relaxation. After relaxation we find all links at zero force and identify them with links that have unbound their nodes. To account for rebinding and to maintain the network's connected structure, we reset those links'  $x_o$  parameters to their new relaxed length, equivalent to assuming the link rebinds rapidly at negligible tension.

To verify that our simplified network geometry is capable of producing a self-organized distribution of near-critical tensions, we first investigate the  $T=0$  limit of the unfolding simulation (i.e., without Bell unfolding). In that case, the network configuration depends only on the strain,  $\gamma$ , and the network's geometrical parameters. For small strains, a roughly uniform distribution of link tension develops. For strains,  $\gamma > 0.4$ , links accumulate at tensions somewhat smaller than  $F_c$ , Fig. 2(c). The distribution of link tensions is an increasing function of force over a small range, with a roughly exponential form  $P(F) \sim \exp(F/F_e)$ . As the strain is increased further, the range of forces showing positive slope broadens while maintaining the same slope:  $F_e/F_c \approx 0.4$ . Simulations with explicit actin filament [25] form a broad exponential distribution of cross-links tension, but with a large height  $P_{\max}/P(F=0) \approx 100$ , where  $P_{\max}$  is the peak value of the force probability distribution. Furthermore, the authors show that the shape of the force probability distribution reflects the distribution of mean field spring constants in their highly disordered networks. In contrast, our exponential force distributions have a comparatively modest height  $P_{\max}/P(F=0) \approx 3$ , as in Fig. 2(c). The difference is presumably due to the much narrower distribution of local network spring constants due to the weak Gaussian disorder in our network.

Our thermalized simulations are performed at a constant, controlled strain rate  $\dot{\gamma}$ . Some discussion of our model's relation to the cellular context is in order before proceeding. We suppose that in cells  $\dot{\gamma}$  is caused by molecular motor sliding or filament treadmilling at a roughly constant velocity. Rather than a uniform, pure shear deformation on the cellular scale, a spatially random deformation field with a typical, mesoscopic strain rate  $\dot{\gamma}$  would presumably serve just as well. We further suppose that other active processes continuously "remodel" the network with a turnover rate comparable to  $\dot{\gamma}$ , such that typical network segments are strained to  $\gamma \sim 1$  in a dynamic steady state that replicates the nonsteady behavior of our model at  $\gamma \sim 1$ .

Unlike the athermal simulations, the evolution of thermalized networks is much more complicated, additionally depending on the Bell parameters  $E_B$  and  $\tau_a$  as well as the strain rate  $\dot{\gamma}$ . Estimates of Bell parameters can be obtained from single molecule AFM experiments and give barrier energies of  $E_B \sim 15-30$  for spectrin repeats [28] and  $E_B \sim 25-60$  for Ig domains [29] (in dimensionless  $k_B T$  units). Estimates for the molecular attempt time  $\tau_a$  have a rather large dispersion in the literature, but are typically of order tens of nanoseconds. To be consistent with 100–1000 s estimates for cytoskeletal turnover,  $\dot{\gamma}$  should be in the range  $10^{-3}-10^{-2} \text{ s}^{-1}$ . Our model is thus controlled by two radically different time scales, the ratio of which  $\dot{\gamma}\tau_a$  may be smaller than  $10^{-11}$  in the physiological case. Achieving this separation of time-scales in our simulation was impractical, despite

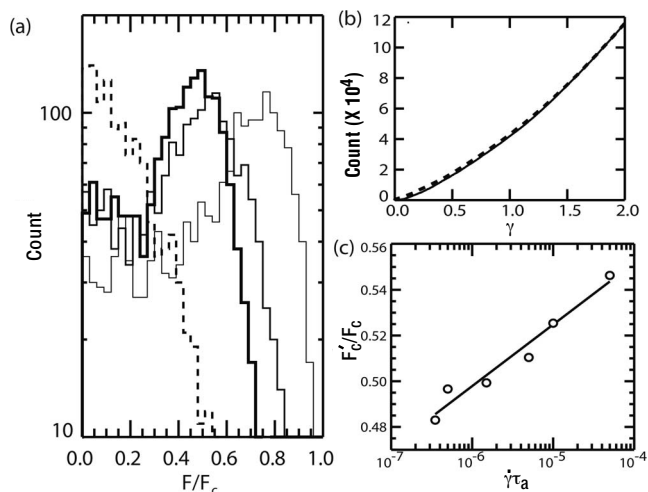


FIG. 3. Force distributions and scaling behavior with Bell-type activated unfolding. (a) Probability distributions of scaled force, determined for strain  $\gamma=1.5$ ,  $E_B=25$ , and  $\tau_a=50$  ns. Solid lines are from unfolding simulations with  $\dot{\gamma}=7,1000 \text{ s}^{-1}$  and the athermal simulation (thin to thick), respectively. The dotted line is from the unbinding simulation at  $\gamma=0.5$ ,  $E_B=25$ ,  $\tau_a=50$  ns, and  $\dot{\gamma}=10 \text{ s}^{-1}$ . (b) The number of unfolded domains as a function of strain. The solid line is during strain application and the dotted line is during strain reversal. (c) Most probable unfolding force as a function of dimensionless strain rate.

the runtime of our algorithm being a strongly sub-linear function of  $(\dot{\gamma}\tau_a)^{-1}$ . In practice, we studied time scale ratios in the range  $10^{-7}-10^{-4}$ .

The results of the thermalized simulation are summarized in Fig. 3. We find that the qualitative form of  $P(F)$  in the thermalized networks is quite similar to the athermal case, but peak at a somewhat smaller force value, defined here as the effective critical force  $F'_c$ . Indeed, the  $P(F)$ 's from all of our thermalized unfolding simulations could be accurately scaled onto one another by rescaling the force axes by their  $F'_c$  values. Unlike the unfolding simulations, the unbinding simulations never showed any accumulation of near critical links, Fig. 3(a), suggesting a fundamentally different type of self-organization behavior for these networks. Interestingly, the number of "unfolded" domains in the network is a monotonic function of network strain, with little dependence on strain rate or hysteresis upon strain reversal, Fig. 3(b).

The effective critical force behavior in the thermalized case has a simple explanation. Bell-type molecules subjected to a constant force loading rate have a well-defined most probable force for unfolding, which is a logarithmic function of the loading rate (i.e., the velocity of an AFM tip) [35]. The constant strain rate  $\dot{\gamma}$  of our model slowly stretches links, potentially leading to an approximately constant loading rate as well. We can identify the resulting most probable link unfolding force with  $F'_c$ , which, as expected, scales logarithmically with  $\dot{\gamma}$ , Fig. 3(c). Links with tensions even slightly smaller than  $F'_c$  have an almost negligible Bell unfolding rate (since  $E_B \gg 1$ ), leading  $P(F)$  to evolve much as an athermal model with "all or nothing" unfolding at critical force  $F'_c$ .

The arrangement of structural molecules on the cusp of conformational change is an ideal configuration for a chemi-

cal mechano-sensor—suggesting that cells may maintain a metabolically costly dynamic cytoskeleton as much for its sensory as its structural functions. Unlike other proposed sensor mechanisms [6,7] that transduce molecular stress, the correspondence of unfolding and network strain suggests the sensing of deformation on the supramolecular scale. In this context, the self-organization of the fragile state provides a physical mechanism for coupling cell-level mechanical strain signals to the molecular-scale biochemical signaling pathways. Most importantly, while the conformational change of single proteins has a significant threshold force that would in principle make them rather insensitive and nonlinear mechanosensors individually, the fragile state automatically situates the molecules near their individual thresholds, causing the number of unfolded domains [as in Fig. 3(b)] to trace deformation in a zero-threshold manner that is nearly linear at finite strain.

To understand how domain unfolding may be transduced, note that many cross-linking species specifically bind a number of signaling proteins, including heat shock proteins, protein kinase C, Ral A, PIP2, PIP3, PI3-kinase, and MEKK1 (for reviews see Refs. [36,37]). If any of these proteins specifically bound (or unbound) to cross-link domains upon forced unfolding, the shear or extensional strain of the network could be transduced to a biochemical signal.

Cells have recently been shown to be able to sense the stiffness of their extracellular matrix (ECM) [3]. What is rarely appreciated is that this ability presumably requires the sensing of both stress and strain. For example, a cell could apply a controlled stress (regulated by a stress-sensor and signaling pathway) to an ECM contact (e.g., a focal adhesion). If the coupling between the focal adhesion and the ECM were sufficiently strong, then the strains of both the ECM and intracellular adhesion structure could be strongly correlated, and the latter could be transduced via a mechanism akin to our serial unfolding fragile network.

Given that the fragile state in our system is driven and maintained by a constant strain rate, it is difficult to compute the rheological response of the network directly, e.g., from the response to a step strain. Large strain steps would significantly affect the network state, while the large amount of random stress noise due to the continual unfolding events would drown out the stresses resulting from small perturbations. Were unfolding events in our network statistically independent, the network's frequency-dependent mechanical response (rheology) could be readily computed from the tension distribution by superposing Maxwell modes [38]. For example, cross-links having tensions near a given force  $F$  would give rise to stress relaxation “modes” at a frequency  $[\tau_B(F)]^{-1}$ . It is straightforward to show that to reproduce the relaxation spectrum corresponding to cell-like power-law rheology, the distribution of crosslink tensions would have to be an increasing exponential function of force, qualitatively resembling that found in the fragile state. Mathematically, this situation resembles that of the soft glassy rheology (SGR) model [26]. Originally developed to describe the unusual mechanical responses and aging behavior of systems with weak ergodicity breaking, such as foams, emulsions and pastes, SGR has more recently been applied to model cell mechanics as well [27]. In SGR, it is supposed that stress

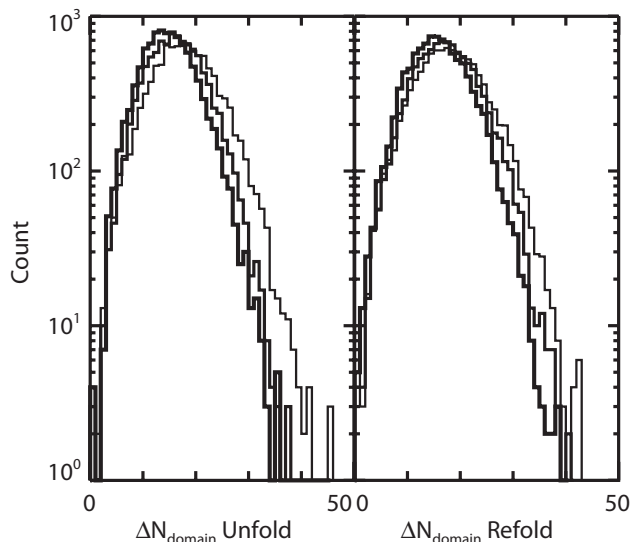


FIG. 4. Histograms for the number of domains either unfolded (left) or refolded (right) over three different strain regimes: 0.25–0.39, 1.4–1.5, and 1.75–1.85 (thin to thick). From low to high strain, the mean of both distributions shifts only slightly, from 17 to 15.

relaxation requires degrees of freedom to surmount barriers having an exponential distribution of energy scales. If those degrees of freedom are statistically independent, and the rate of barrier crossing is a Bell model-like exponential function of the barrier height, the shear modulus in the weakly ergodic state is a weak power law of frequency. In a serial unfolding network in the fragile state, the force lowered energetic barriers to subcritical unfolding may be analogous to the barriers in SGR-like systems. More specifically, the exponential distribution of crosslink tension leads to a SGR-like exponential distribution of effective barrier heights.

Despite the appealing possibility that fragility in serial unfolding networks could explain cells' power-law rheology and other soft glasslike behaviors, it is clear that the required statistical independence of cross-link ruptures is not satisfied in our simulated network. In fact, we find that when unfolding a single subcritical link in the fragile state typically 30 links change their degree of unfolding, (with about half increasing and half decreasing), independent of strain, Fig. 4. While a significant degree of cooperativity, 30 links represent only 2% of the total, and we find they do not span the system. Physically, such cooperativity implies that a given subcritical link is statistically much more likely to be critically unfolded by the transient stress due to a nearby link unfolding than by its own Bell-type activation. On a more positive note, mean field calculations [24,25] suggest that the fragile state can form in the absence of any cooperativity and that more realistic network geometries can have far smaller cooperativity. We suspect that the latter point is related to the degree of cross-link connectedness. In our network, connecting nodes share only five or six links. In a more realistic network [25], actin filaments can plausibly serve as nodes to distribute stress among dozens of cross-links, leading a single unfolding event to be a much smaller perturbation to the stress of neighboring links.

While Maxwell mode superposition does not allow us to compute the rheology of our network, it does allow us to estimate characteristic frequencies of the response. The weak power-law rheology of cells has been observed to extend up to at least  $\omega \sim O(10^4) \text{ s}^{-1}$ , or 6–7 orders of magnitude faster than the characteristic time for the strain process driving the fragile state  $\dot{\gamma}$ . It is not obvious *a priori* that such slow strain can excite and maintain such rapidly relaxing modes. The fastest decaying modes in the network should have a characteristic frequency  $\omega_{\max} \approx 1/\tau_B[F'_c(\dot{\gamma})]$ ; above that frequency, stress relaxation in the network should be negligible and the network should be elastic (neglecting modes related to filament undulations). Examining our simulation results, we find that the maximum frequency is a very slow function of the strain rate  $\omega_{\max} \sim \dot{\gamma}^b \tau_a^{b-1}$ , with  $b \approx 0.18$ . In other words, for  $\dot{\gamma} \tau_a \approx 10^{-11}$ , then  $\omega_{\max}$  should be about 100 times lower than the attempt frequency for unfolding,  $\tau_a^{-1} \sim O(10^5) \text{ s}^{-1}$ , a value compatible with current experimental limits. Indeed, the finding that thermalized serial unfolding networks are able to convert very low-frequency input energy to excite very high frequency relaxation modes is perhaps the most surprising and interesting result of this work.

Models of networks containing serial unfolding elements have the potential to reproduce not only cells' unusual dynamic shear modulus, but also to explain how a filamentary polymer gel can display the weakly ergodic behavior typi-

cally associated with foams and pastes. Obviously, developing this idea will require an extensive effort to find networks having the correct geometry, fragility, and cooperativity. Here we show that a simplified network displays fragility that is robust under thermalization. While our network formulation is unlikely to display power-law rheology, we find that the fragile state is remarkably effective at converting mechanical energy at low frequency to very rapidly decaying modes, as required by comparison with experiment. At the very least, such networks provide a novel mechanism for cells to sense mesoscale deformation of different subcellular structures as well as ECM stiffness. This hypothesis makes biochemically testable predictions: that some cross-link species should be partially unfolded under normal physiological conditions, and that their unfolding should increase with cell deformation [7,8]. Such biochemical studies, combined with future network simulations hold the prospect of a cytoskeleton model grounded in polymer and single-molecule biophysics.

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