



ELSEVIER

The cell as a material

Karen E Kasza, Amy C Rowat, Jiayu Liu, Thomas E Angelini, Clifford P Brangwynne, Gijsje H Koenderink and David A Weitz

To elucidate the dynamic and functional role of a cell within the tissue it belongs to, it is essential to understand its material properties. The cell is a viscoelastic material with highly unusual properties. Measurements of the mechanical behavior of cells are beginning to probe the contribution of constituent components to cell mechanics. Reconstituted cytoskeletal protein networks have been shown to mimic many aspects of the mechanical properties of cells, providing new insight into the origin of cellular behavior. These networks are highly nonlinear, with an elastic modulus that depends sensitively on applied stress. Theories can account for some of the measured properties, but a complete model remains elusive.

Addresses

Department of Physics & DEAS, Harvard University, Cambridge, MA 02138 USA

Corresponding author: Weitz, David A (weitz@deas.harvard.edu)

Current Opinion in Cell Biology 2007, **19**:101–107

This review comes from a themed issue on
Cell structure and dynamics
Edited by Daniel P Kiehart and Kerry Bloom

Available online 15th December 2006

0955-0674/\$ – see front matter
© 2006 Elsevier Ltd. All rights reserved.

DOI [10.1016/j.ceb.2006.12.002](https://doi.org/10.1016/j.ceb.2006.12.002)

Introduction

Cells are highly dynamic: they crawl, change shape and divide. In many critical biological processes, cells both exert and respond to forces in their surroundings; the mechanical properties of the cell are intimately related to this behavior. Cells also continually remodel their internal structure and thereby change their mechanical properties. An integrated understanding of cell structure and mechanics is thus essential for elucidating many fundamental aspects of cell behavior, from motility to differentiation and development. Here we focus on the mechanical properties of cells and review recent developments in our understanding of the cell as a material.

A variety of experimental techniques show that cells have both elastic and viscous characteristics, and thus are viscoelastic materials: their stiffness is similar to Jello, but they continue to slowly deform under a steady stress (Figure 1a). Unlike most conventional materials, cells are highly nonlinear; their elastic modulus depends on the

degree of applied or internal stress (Figure 2) [1^{••}]. Moreover, their elastic behavior depends on the mechanical properties of their environment [2].

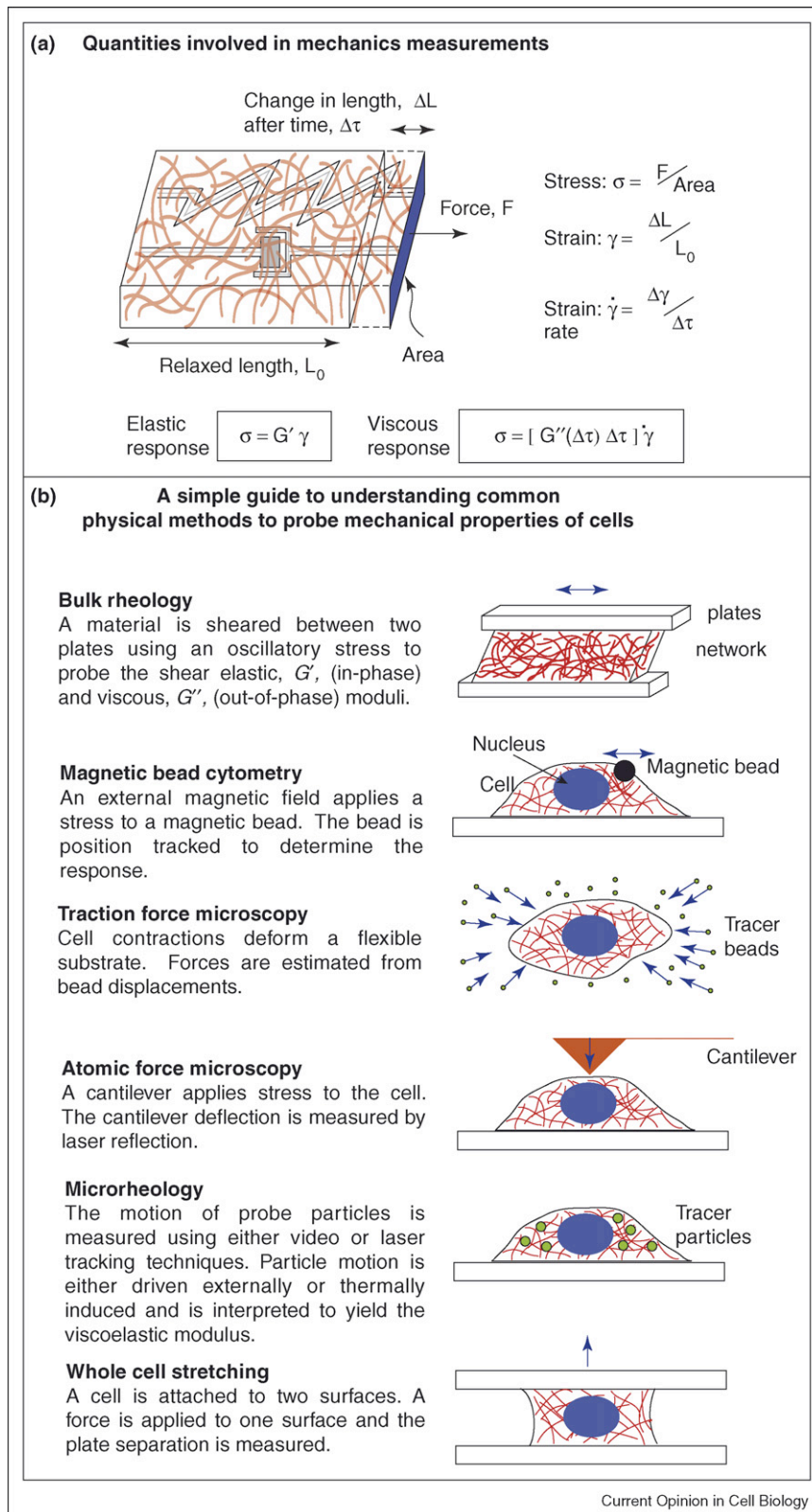
The mechanical properties of the cell are largely determined by the cytoskeleton, a biopolymer network consisting of three major components: filamentous actin (F-actin), intermediate filaments and microtubules (Figure 3a). In addition, a myriad of filament crosslinker, motor and regulatory proteins play a critical role in cytoskeletal structure and dynamics and hence in the mechanical properties of the cytoskeleton. The cytoskeleton is a complex, heterogeneous and dynamic structure, which makes the study of its properties extremely difficult. The two major approaches to this problem are *in vitro* studies of model networks designed to mimic the properties of individual components of the cytoskeleton, and studies of the mechanical properties of cells themselves.

Reconstituted cytoskeletal networks

A major advantage of reconstituted networks is that their viscoelastic properties can be probed by traditional engineering approaches [3[•]], as well as by more sophisticated optical methods; by measuring the time-dependent response to an imposed stress or strain, both the elastic and viscous properties can be determined. Networks of F-actin are among the most widely studied reconstituted systems. As with the other cytoskeletal filaments, F-actin is a semi-flexible polymer, neither completely flexible, like more traditional synthetic polymers, nor perfectly rigid. Instead, the filaments are soft enough to have some thermally induced shape fluctuations that play an important role in their elasticity. The effects of thermal fluctuations are particularly apparent in the network elasticity at the shortest timescales, leading to a characteristic time dependence [4]; the same behavior was also recently observed in cells [5^{••},6[•]]. Other recent measurements of F-actin networks demonstrate the important role of filament length [7] and additional relaxation mechanisms specific to semi-flexible filaments [8]. While earlier studies elucidate the behavior of solutions of entangled F-actin alone, current efforts focus primarily on the effects of crosslinking proteins and other actin-binding proteins (Figure 3b). The elasticity of the resultant crosslinked networks has a different physical origin, and can depend sensitively on both actin and crosslinker concentration [9–11,12^{••},13[•]]. Studies of crosslinked networks are likely to remain an area of active investigation.

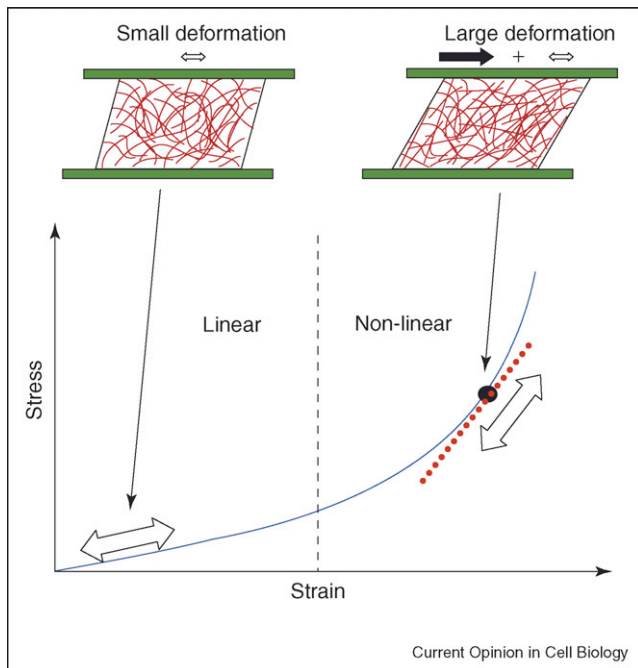
The semi-flexible nature of the filaments constituting these networks is particularly important under increasing

Figure 1



Mechanics of biopolymer networks and cells. **(a)** Quantities involved in mechanics measurements. Many materials have both elastic and viscous properties. The elasticity of biopolymer networks makes them resist deformation like a simple spring (grey, upper) for which the energy of deformation is stored in the material regardless of time; to quantify this we measure an elastic modulus, G' , which is analogous to a spring constant. The viscosity of

Figure 2



Understanding linear versus nonlinear rheology and stress-stiffening. Under small deformations, the stress is proportional to the strain, and the material is said to be in the linear regime of its mechanical response. This is usually probed by applying a small oscillatory stress or strain to the material (white double-headed arrow) and measuring the response. However, under larger deformations, the stress for many biological materials increases more rapidly with applied strain. Here the material is said to be in the nonlinear regime. This is usually probed by applying a large, steady stress that brings the material into the nonlinear regime (thick black arrow, top right), and then measuring the stiffness by applying an additional small, oscillatory stress or strain (white double-headed arrow) and measuring the response. The stiffness is reflected by the local slope (dotted line) of the stress-strain relationship, referred to as the differential modulus, K^* .

applied stress. For most materials, the elastic constant is independent of the applied stress. By contrast, networks of semi-flexible polymers often exhibit an unusual property: with increasing applied stress, their elastic modulus increases (Figure 3c) [9,14^{••}]. This is called stress-stiffening and typically reflects individual filament behavior; at low extensions, filament elasticity originates from thermal fluctuations, while at higher extensions, thermal fluctuations are ‘pulled out’, leading to a dramatic increase in effective filament elasticity (i.e. stiffening) [9,11]. To accurately measure such nonlinear network behavior

requires different techniques: for example, a steady stress is applied to the material, and the modulus is determined from the response to a small, superposed oscillatory stress (Figure 2) [9–11,12^{••},13[•]].

The stress-stiffening of biopolymer networks has important implications: the magnitude of their linear elasticity is typically orders of magnitude less than that of cells; however, when prestressed into the nonlinear regime, the elasticity of these networks dramatically increases, approaching that of cells [10,12^{••}]. This suggests that cells themselves are prestressed into a nonlinear regime, presumably by molecular motors such as myosin. It would be particularly interesting to test the role of myosin in *in vitro* networks [15].

Much less is known about the mechanics of networks reconstituted from other cytoskeletal proteins. The behavior of single intermediate filaments under applied stress [16–18] may help to explain the observed behavior of their networks [14^{••}]. Studies of the mechanical response of isolated microtubules suggests that their rigidity and bending are affected by internal motions of the tubulin subunits [19]; how this affects microtubule network properties is yet to be determined. Future work is likely to continue to focus on networks consisting of more than one cytoskeletal component to explore their composite material properties [20,21,22^{••}].

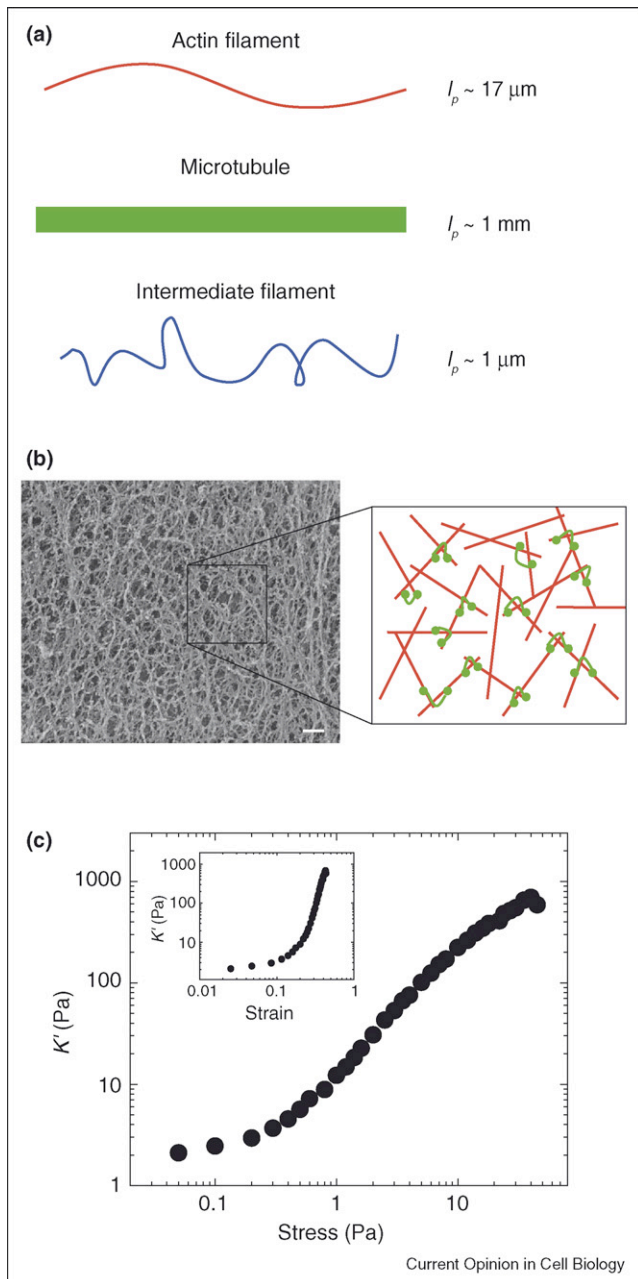
Measurements of cell mechanics

The mechanical properties of cells are incredibly rich; understanding them is challenging as there is a diversity of experimental techniques that probe different parts of the cell and report varying responses (Figure 1b). All of these techniques entail the measurement of a deformation in response to a force. While each method probes a different aspect of cell mechanics, together they are beginning to provide a more unified understanding.

The structural heterogeneity and region-to-region variation of cell properties make methods to probe local mechanical response essential. The local viscoelastic properties of a single cell can be probed through micro-indentation by atomic force microscopy (AFM) [23–26]. Alternatively, a local stress can be applied to a specific region of the cell by twisting or pulling a small magnetic bead that is attached to the cell [5^{••},27–29,30[•],31,32]. In magnetic twisting cytometry (MTC), the resultant bead displacement is measured either with video microscopy

Figure 1 Legend (continued) biopolymer networks allows them to flow as a fluid, leading to resistance that depends on the rate of deformation like in a dashpot (grey, lower) for which the energy put into deformation is dissipated or lost; a viscous modulus, G'' , characterizes this. By measuring the material's response to an applied stress as a function of time, the two contributions can be distinguished. Typically, G' and G'' specifically refer to the moduli measured from an oscillatory shear deformation — see “Bulk rheology” in (b); here we use them to denote simply the elastic and viscous responses for some mechanical measurement. The techniques described in (b) provide different ways of probing the relationship between stress and strain to determine both the elastic and viscous properties of the material. (b) A simple guide to understanding common physical methods to probe mechanical properties of cells.

Figure 3



From filaments to networks. **(a)** Schematic illustrations of the filaments that constitute the cytoskeleton: F-actin, microtubules and intermediate filaments. Denoted here is the persistence length, l_p , the length scale above which these thermally fluctuating filaments appear to be floppy. **(b)** Left: *in vitro* network of F-actin (1 mg/ml) filaments capped with gelsolin (1:555 molar ratio to actin) and crosslinked with filamin A (1:50 molar ratio to actin). The sample is fixed, rotary-shadowed, and imaged by transmission electron microscopy. Scale bar = 200 nm. (Courtesy of JH Hartwig.) Right: schematic illustration of a crosslinked network. The actin filaments are much shorter in length than their persistence length, and hence are nearly rigid. The crosslinkers can themselves be flexible. **(c)** Bulk rheology measurement of a reconstituted actin network (1 mg/ml) crosslinked with filamin A (1:50 molar ratio to actin). The differential elastic modulus, K' , is measured as a function of stress (Figure 1). K' increases nearly

or, to even higher precision, with laser particle tracking [5**]. While this technique probes local mechanics, it suffers from uncertainties in the nature of the bead attachment to the cell, which makes determining a true magnitude for the elastic and viscous moduli difficult.

Other techniques rely on endogenous structures; for example, local response is probed by the motion or deformation of microtubules [22**], actin filaments [33**,34], mitochondria and other subcellular structures (Figure 4) [5**,34–36]. These techniques also probe the transmission of force through the cell, and highlight the complexity of the mechanical coupling between different structural components. In addition, the mechanical properties of the cell nucleus are probed using micropipette aspiration coupled to confocal microscopy; these measurements show that the nuclear envelope behaves as an elastic shell [37,38**], which can contribute to the elasticity of the whole cell.

Local material properties of cells are also investigated using measurements of the motion of probe particles within a cell. However, recent work [5**] clearly shows the potential pitfalls in the interpretation of these results. To determine the elastic constant, the particle motion is assumed to be driven exclusively by thermal fluctuations; however, the activity of motor proteins and other non-equilibrium processes in cells also contribute to motion. Not considering these effects can produce erroneous results [39,40].

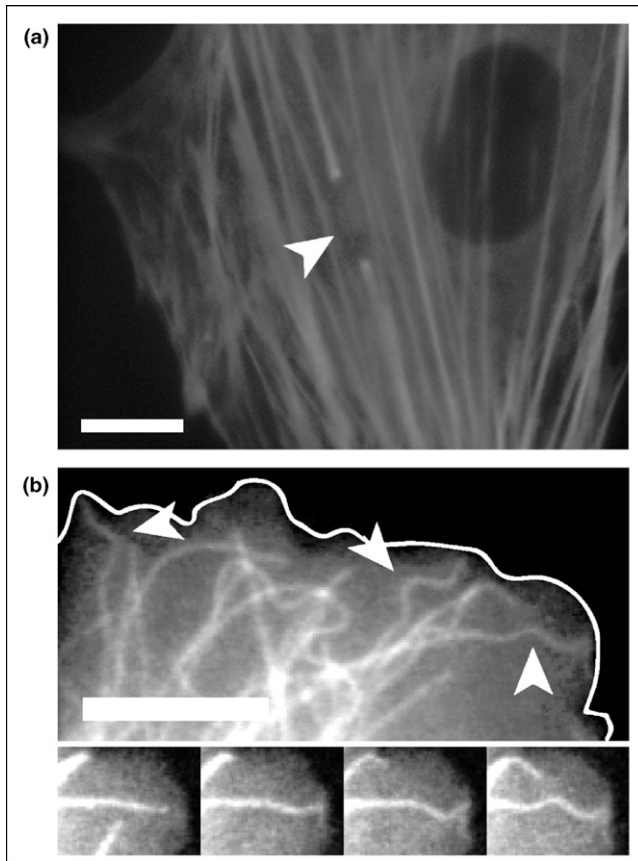
Recent experiments have highlighted the importance of the fluid properties of the cell. Any motion of the networks also entails motion of the water in which they are embedded, and this will contribute to the overall response [41].

The results from all of these techniques are beginning to provide a consistent picture: at timescales varying between a fraction of a second and several tens of seconds, the cell is a predominantly elastic material. At timescales shorter than a fraction of a second, the response reflects the effects of individual filaments and the elasticity increases [5**,6*]. At timescales of >30 seconds, the effects of cell remodeling [42] lead to additional relaxation [30*]. External forces elicit active responses in cells over timescales of seconds to tens of seconds, such as changes in focal adhesion composition, contractility and cell stiffness [2,28,43].

Viscoelastic response can also be directly determined by deforming the whole cell [1**,44,45]. Recent experiments demonstrate that the elasticity of a whole cell increases

linearly with stress, stiffening by a factor of 350 before breaking. Inset: same data plotted as a function of strain, highlighting the dramatic stiffening with strain.

Figure 4



Cells are complex materials with components under tension and compression. **(a)** Stress fibers in cells stained with EYFP-actin are severed by laser nanoscissors. After abscission, single stress fiber bundles snap back, exhibiting tension. Scale bar = 10 μm . Reprinted with permission from [33]. **(b)** Although microtubules are very rigid, in cells they are highly bent, indicating large internal stresses. These stresses are often compressive, leading to a characteristic short wavelength buckling response. Time sequence shows a buckling microtubule (left to right, 5 s between images). Scale bar = 5 μm . Reprinted with permission from [22].

dramatically when it is stretched [1^{••}], consistent with earlier experiments relating cell elasticity to internally generated prestress [46] and studies of the nonlinear material properties of reconstituted networks [10,12^{••}]. These observations suggest that prestress in the cytoskeleton may be a key parameter that determines cell elasticity. This prestress can be determined using traction force microscopy, where the internal contractile stress in the cell is partially balanced by a measurable deformation of the substrate [33^{••},41,46]. Alternatively, prestress is determined by monitoring the retraction of a cell after detachment from the substrate [47]. All prestress measurements to date are restricted to cells grown on surfaces; traction force measurements in more complex, three-dimensional environments are only now emerging [41].

The prestress and elasticity of the cell, as well as its internal structure, are responsive to external cues. Recent work shows that in response to external forces applied through magnetic beads, cells stiffen in some cases [28], but weaken in others [30[•]]. There is also evidence that prestress impacts cell adhesion [43], as well as the propagation of stresses within the cell [36]. The relationship between the elasticity of the cell and its environment will continue to be a topic of active interest.

Modeling cell mechanics

The highly complex and heterogeneous structure of the cell makes modeling its mechanical properties very difficult. A complete model should account for all components that contribute to the mechanics of the cell, as well as the interactions between these components that result in the full ‘system’ behavior. There are many models that describe at least some properties, and there has been extensive work on several of these models during the past two years.

One widely debated model is the ‘tensegrity’ model [33^{••}]. While the details of the model have been described in many ways, the central principle is that some components in the cell are under tension, and these forces are balanced by other components under compression. Recent results have confirmed that components of the cytoskeletal network are under tension: when stress fibers are cut with a laser, they snap back (Figure 4a) [33^{••}]. Moreover, traction-force microscopy clearly demonstrates the internal tension in the cell [33^{••},41,46]. Concomitant with this, recent studies of microtubules in cells confirm that they bear compressive loads; these can be unexpectedly large because the surrounding cytoskeleton structurally reinforces the microtubules (Figure 4b) [22^{••}]. The tensegrity model highlights the role of prestress in determining cell elasticity.

A second model to describe cell elasticity that has gained considerable traction is the ‘soft glassy rheology’ (SGR) model [6,30[•]]. This is a conceptual model for soft solids that suggests the material is composed of an elastic solid with some relaxation process driven by non-thermal stress fluctuations, such as those generated by molecular motors. The predicted mechanical response displays a characteristic timescale dependence that is set by the effective temperature of these fluctuations. Recent results using MTC confirm the predictions of the SGR model at intermediate timescales, but show a deviation at short timescales where the response begins to reflect the behavior of single filaments [6[•]]. Moreover, tracer beads attached to cell surfaces exhibit large scale motions, indicating structural rearrangements due to non-thermal relaxation events, consistent with the SGR model [30[•]]. Interestingly, applying a large shear stress by MTC temporarily softens the cell, analogous to the shear-induced melting and rejuvenation that typifies many

traditional soft glasses. Further investigations will shed light on the nature of the non-thermal stress fluctuations emphasized by the SGR model.

There are many more 'engineering' approaches for understanding the mechanics of the cell. Most of these are based on finite-element or other computer-generated solutions to constitutive relations [48]. While such approaches do have some value, their predictive power is ultimately limited by the exact input used to describe the components of the cell. Nevertheless, such models are essential in the interpretation of some experimental measurements.

Models based on the physics of semi-flexible polymers continue to provide an excellent description of the behavior of reconstituted networks [4,8–11,12**,14**]. Further refinements are likely to capture the behavior of networks formed with specific crosslinkers and with motor proteins, and may ultimately describe the properties of the cell.

A successful theory must incorporate the recent experimental evidence highlighting the importance of nonlinear mechanics and internal pre-stress. This requires refining the non-equilibrium components of current theories or developing completely new approaches.

Conclusions

Cells are clearly very complex and dynamic materials whose mechanical properties are only now beginning to be understood. An array of techniques developed to probe cell mechanics show they are nonlinear, viscoelastic materials. Arriving at a consensus between all measurement techniques and all models of cell properties remains a challenge. Our knowledge will be advanced in part by continued studies of reconstituted *in vitro* systems of increasing complexity, as well as by the development of increasingly sophisticated techniques to directly probe cell mechanics. Ultimately our understanding of the material properties of the cell will help elucidate the interplay between mechanics and biochemistry that regulates functional cell behavior.

Acknowledgements

The authors were supported by NSF (DMR-0602684) and the Integrated Training Program in Biomechanics (DGE-0221682) (CPB), NDSEG (KEK), European Marie Curie Fellowship (FP6-2002-Mobility-6B, Contract No. 8526) (GHK), and the Human Frontiers Science Program (ACR, DAW). We thank Dr. J.H. Hartwig for providing the electron microscopy image of the actin network.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Fernandez P, Pullarkat PA, Ott A: **A master relation defines the nonlinear viscoelasticity of single fibroblasts.** *Biophys J* 2006, **90**:3796-3805.
2. Jiang GY, Huang AH, Cai YF, Tanase M, Sheetz MP: **Rigidity sensing at the leading edge through $\alpha v \beta 3$ Integrins and RPTP α .** *Biophys J* 2006, **90**:1804-1809.
3. Bausch AR, Kroy K: **A bottom-up approach to cell mechanics.**
 - *Nature Physics* 2006, **2**:231-238.

This review paper gives an overview of the strategy to investigate cell mechanics based on reconstituting functional cytoskeletal modules from purified proteins.
4. Koenderink GH, Atakhorrami M, MacKintosh FC, Schmidt CF: **High-frequency stress relaxation in semiflexible polymer solutions and networks.** *Phys Rev Lett* 2006, **96**:138307.
5. Hoffman BD, Massiera G, Van Citters KM, Crocker JC: **The consensus mechanics of cultured mammalian cells.** *Proc Natl Acad Sci USA* 2006, **103**:10259-10264.

A combination of measurement techniques provides a comprehensive probe of the mechanical properties of the cell, helping the authors in the first attempt to probe the contributions of different structural components. This paper clearly elucidates both the strengths and weaknesses of these measurement techniques.

6. Deng L, Treppe X, Butler JP, Millet E, Morgan KG, Weitz DA, Fredberg JJ: **Fast and slow dynamics of the cytoskeleton.** *Nat Mater* 2006, **5**:636-640.

The authors use MTC to probe the mechanical properties of the cell and show that the nearly pure elastic behavior that is characteristic of the SGR model is restricted to intermediate timescales. At short timescales, a different elastic behavior is observed, consistent with the properties of individual filaments, and similar to that observed in *in vitro* networks.

7. Liu J, Gardel ML, Kroy K, Frey E, Hoffman BD, Crocker JC, Bausch AR, Weitz DA: **Microrheology probes length scale dependent rheology.** *Phys Rev Lett* 2006, **96**:118104.
8. Gardel ML, Valentine MT, Crocker JC, Bausch AR, Weitz DA: **Microrheology of entangled F-actin solutions.** *Phys Rev Lett* 2003, **91**:158302.
9. Gardel ML, Shin JH, MacKintosh FC, Mahadevan L, Matsudaira P, Weitz DA: **Elastic behavior of cross-linked and bundled actin networks.** *Science* 2004, **304**:1301-1305.
10. Gardel ML, Nakamura F, Hartwig J, Crocker JC, Stossel TP, Weitz DA: **Stress-dependent elasticity of composite actin networks as a model for cell behavior.** *Phys Rev Lett* 2006, **96**:088102.
11. Gardel ML, Shin JH, MacKintosh FC, Mahadevan L, Matsudaira PA, Weitz DA: **Scaling of F-actin network rheology to probe single filament elasticity and dynamics.** *Phys Rev Lett* 2004, **93**:188102.
12. Gardel ML, Nakamura F, Hartwig JH, Crocker JC, Stossel TP, Weitz DA: **Prestressed F-actin networks cross-linked by hinged filamins replicate mechanical properties of cells.** *Proc Natl Acad Sci USA* 2006, **103**:1762-1767.

Rheological measurements of *in vitro* actin networks crosslinked with filamin show that there is a dramatic increase of the elastic constant with applied prestress, resulting in values comparable to those reported in cells. This suggests that the prestress typically found in cells plays a critical role in determining their elastic modulus.

13. Wagner B, Tharmann R, Haase I, Fischer M, Bausch AR: **Cytoskeletal polymer networks: molecular structure of crosslinkers determine macroscopic properties.** *Proc Natl Acad Sci USA* 2006, **103**:13974-13978.

This paper investigates the mechanics of actin networks crosslinked with different isoforms of *Dictyostelium* filamin, and highlights the sensitivity of the mechanical properties to the specific character of the crosslinker.

14. Storm C, Pastore JJ, MacKintosh FC, Lubensky TC, Janmey PA: **Nonlinear elasticity in biological gels.** *Nature* 2005, **435**:191-194.

The authors show that many different biopolymer networks all exhibit a universal behavior in their stress stiffening. They interpret these data with a model based on the properties of the individual filaments constituting the network.

15. McGrath JL: **Cell mechanics: FilaminA leads the way.** *Curr Biol* 2006, **16**:R326-R327.

16. Kiss B, Karsai A, Kellermayer MS: **Nanomechanical properties of desmin intermediate filaments.** *J Struct Biol* 2006, in press.
17. Guzman C, Jeney S, Kreplak L, Kasas S, Kulik AJ, Aebi U, Forro L: **Exploring the mechanical properties of single vimentin intermediate filaments by atomic force microscopy.** *J Mol Biol* 2006, **360**:623-630.
18. Kreplak L, Bar H, Leterrier JF, Herrmann H, Aebi U: **Exploring the mechanical behavior of single intermediate filaments.** *J Mol Biol* 2005, **354**:569-577.
19. Pampaloni F, Lattanzi G, Jonas A, Surrey T, Frey E, Florin EL: **Thermal fluctuations of grafted microtubules provide evidence of a length-dependent persistence length.** *Proc Natl Acad Sci USA* 2006, **103**:10248-10253.
20. Parekh SH, Chaudhuri O, Theriot JA, Fletcher DA: **Loading history determines the velocity of actin-network growth.** *Nat Cell Biol* 2005, **7**:1119-1123.
21. Claessens MMAE, Tharmann R, Kroy K, Bausch AR: **Microstructure and viscoelasticity of confined semiflexible polymer networks.** *Nature Physics* 2006, **2**:186-189.
22. Brangwynne CP, MacKintosh FC, Kumar S, Geisse NA, Talbot J, Mahadevan L, Parker KK, Ingber DE, Weitz DA: **Microtubules can bear enhanced compressive loads in living cells because of lateral reinforcement.** *J Cell Biol* 2006, **173**:733-741.
Microtubules display short wavelength buckling in response to naturally occurring compressive loads within the cell. This response indicates structural reinforcement from the surrounding cytoskeleton.
23. Mahaffy RE, Park S, Gerde E, Kas J, Shih CK: **Quantitative analysis of the viscoelastic properties of thin regions of fibroblasts using atomic force microscopy.** *Biophys J* 2004, **86**:1777-1793.
24. Park S, Koch D, Cardenas R, Kas J, Shih CK: **Cell motility and local viscoelasticity of fibroblasts.** *Biophys J* 2005, **89**:4330-4342.
25. Alcaraz J, Buscemi L, Grabulosa M, Trepast X, Fabry B, Farre R, Navajas D: **Microrheology of human lung epithelial cells measured by atomic force microscopy.** *Biophys J* 2003, **84**:2071-2079.
26. Rosenbluth MJ, Lam WA, Fletcher DA: **Force microscopy of nonadherent cells: a comparison of leukemia cell deformability.** *Biophys J* 2006, **90**:2994-3003.
27. Deng LH, Fairbank NJ, Cole DJ, Fredberg JJ, Maksym GN: **Airway smooth muscle tone modulates mechanically induced cytoskeletal stiffening and remodeling.** *J Appl Physiol* 2005, **99**:634-641.
28. Matthews BD, Overby DR, Mannix R, Ingber DE: **Cellular adaptation to mechanical stress: role of integrins, Rho, cytoskeletal tension and mechanosensitive ion channels.** *J Cell Sci* 2006, **119**:508-518.
29. Puig-de-Morales M, Millet E, Fabry B, Navajas D, Wang N, Butler JP, Fredberg JJ: **Cytoskeletal mechanics in adherent human airway smooth muscle cells: probe specificity and scaling of protein-protein dynamics.** *Am J Physiol Cell Physiol* 2004, **287**:C643-C654.
30. Bursac P, Lenormand G, Fabry B, Oliver M, Weitz DA, Viasnoff V, Butler JP, Fredberg JJ: **Cytoskeletal remodelling and slow dynamics in the living cell.** *Nat Mater* 2005, **4**:557-561.
The contribution of nonthermal stress fluctuations is probed by bead cytometry and microrheological techniques, suggesting that the rheological response of cells reflects non-equilibrium physical behavior. The results are interpreted in terms of the SGR model.
31. Coughlin MF, Puig-de-Morales M, Bursac P, Mellema M, Millet E, Fredberg JJ: **Filamin-A and rheological properties of cultured melanoma cells.** *Biophys J* 2006, **90**:2199-2205.
32. Lenormand G, Millet E, Fabry B, Butler J, Fredberg J: **Linearity and time-scale invariance of the creep function in living cells.** *J R Soc Interface* 2004, **1**:91-97.
33. Kumar S, Maxwell IZ, Heisterkamp A, Polte TR, Lele TP, Salanga M, Mazur E, Ingber DE: **Viscoelastic retraction of single living stress fibers and its impact on cell shape, cytoskeletal organization, and extracellular matrix mechanics.** *Biophys J* 2006, **90**:3762-3773.
Laser ablation is used to sever stress fibers in cells. The retraction of these severed fibers confirms that these structural components are under significant tension.
34. Wang N, Suo Z: **Long-distance propagation of forces in a cell.** *Biochem Biophys Res Commun* 2005, **328**:1133-1138.
35. Lau AWC, Hoffman BD, Davies A, Crocker JC, Lubensky TC: **Microrheology, stress fluctuations, and active behavior of living cells.** *Phys Rev Lett* 2003, **91**:198101.
36. Hu S, Wang N: **Control of stress propagation in the cytoplasm by prestress and loading frequency.** *Mol Cell Biomech* 2006, **3**:49-60.
37. Rowat AC, Foster LJ, Nielsen MM, Weiss M, Ipsen JH: **Characterization of the elastic properties of the nuclear envelope.** *J R Soc Interface* 2005, **2**:63-69.
38. Rowat AC, Lammerding J, Ipsen JH: **Mechanical properties of the cell nucleus and the effect of emerin deficiency.** *Biophys J* 2006, **91**:1-16.
A combination of micropipette aspiration and confocal imaging is used to probe the response of the nucleus to deformations in cells. This highlights the importance of the mechanical properties of the nucleus.
39. Tseng Y, Kole TP, Lee JS, Fedorov E, Almo SC, Schafer BW, Wirtz D: **How actin crosslinking and bundling proteins cooperate to generate an enhanced cell mechanical response.** *Biochem Biophys Res Commun* 2005, **334**:183-192.
40. Lee JS, Panorchan P, Hale CM, Khatau SB, Kole TP, Tseng Y, Wirtz D: **Ballistic intracellular nanorheology reveals ROCK-hard cytoplasmic stiffening response to fluid flow.** *J Cell Sci* 2006, **119**:1760-1768.
41. Mierke CT, Paranhos Zitterbart D, Koch T, Fabry B: **Kraftmessung an Zellen in 2D und 3D.** *BIOspektrum (Heidelb)* 2006, **12**:390-391.
42. Danuser G, Waterman-Storer CM: **Quantitative fluorescent speckle microscopy of cytoskeleton dynamics.** *Annu Rev Biophys Biomol Struct* 2006, **35**:361-387.
43. Lele TP, Pendse J, Kumar S, Salanga M, Karavitis J, Ingber DE: **Mechanical forces alter zyxin unbinding kinetics within focal adhesions of living cells.** *J Cell Physiol* 2006, **207**:187-194.
44. Desprat N, Richert A, Simeon J, Asnacios A: **Creep function of a single living cell.** *Biophys J* 2005, **88**:2224-2233.
45. Wottawah F, Schinkinger S, Lincoln B, Ananthakrishnan R, Romeyke M, Guck J, Kas J: **Optical rheology of biological cells.** *Phys Rev Lett* 2005, **94**:098103.
46. Wang N, Tolic-Norrelykke IM, Chen J, Mijalovich SM, Butler JP, Fredberg JJ, Stamenovic D: **Cell prestress. I. Stiffness and prestress are closely associated in adherent contractile cells.** *Am J Physiol Cell Physiol* 2002, **282**:C606-C616.
47. Griffin MA, Engler AJ, Barber TA, Healy KE, Sweeney HL, Discher DE: **Patterning, prestress, and peeling dynamics of myocytes.** *Biophys J* 2004, **86**:1209-1222.
48. Herant M, Marganski WA, Dembo M: **The mechanics of neutrophils: synthetic modeling of three experiments.** *Biophys J* 2003, **84**:3389-3413.