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Microtubule Mechanics: A Little Flexibility Goes a Long Way

Microtubules are the least flexible of the cytoskeletal filaments, yet they are occasionally seen to be severely buckled in cells. A recent analysis suggests these buckles are evidence of high contractile forces throughout the cytoplasm, and that the other elements of the cytoskeleton laterally reinforce microtubules to help prevent their collapse.

James L. McGrath

Cellular microtubules do not bend easily. Unlike actin microfilaments and intermediate filaments which fill the cytoplasm as entangled meshworks, microtubules often radiate from perinuclear regions to cell margins as individual rods. Flexural rigidity is important for microtubules to function as superhighways for molecule and organelle transport through the cytoplasm, and for their function as dynamic struts that push and pull on chromosomes from a distance during mitosis. The microtubule's flexural stiffness derives from its form: as a hollow tube, the microtubule follows the engineering design principle that structures designed to resist bending should distribute material away from their central axis [1].

Indeed, the microtubule's resistance to bending is 100 times greater than that of the more compact actin filament, despite the fact that the actin and tubulin subunits are mechanically similar materials [2]. With both microtubule structure and function implying flexural stiffness, it is curious that microtubules can occasionally be found in highly bent configurations inside of cells [3].

In a recent study, Brangwynne et al. [3] investigated the mechanical implications of microtuble curvatures observed in living cells. Because thermal forces alone are too small to impart significant curvature to microtubules, an arching microtubule contour implies that it is being deformed by transverse loads or has buckled from compression. From classical structural analysis of column buckling [4], it is expected that microtubules will buckle under piconewton compressive loads generated by polymerization and depolymerization [5], but the characteristic length of the waveform should be tens of microns long. While this analysis can account for the appearance of slowly arching microtubules connecting polarized centrioles to chromosomes aligned at the equator of a mitotic spindle, Brangwynne et al. [3] noted that microtubules in the cytoplasm of interphase cells often have highly localized bends with wavelengths of only a few microns. Using fluorescently labeled tubulin, the group documented short wavelength buckling of microtubules under three different conditions: first, when growing microtubules collided with the plasma membrane; second, when peripheral microtubules were actively compressed by deforming the plasma membrane with a microneedle; and third, when cells executed myosin-based contractions.

The observations of Brangwynne et al. [3] raise two questions: First, why does this form of buckling

occur only in certain regions of a microtubule? And second, what force levels must be present to generate shortwave buckling? The authors hypothesized that the answer to the first question was lateral reinforcement: microtubules physically connect to networks of actin and intermediate filaments throughout the cytoplasm and these connections might provide additional support to microtubules.

To test this hypothesis, Brangwynne et al. [3] treated cells with the actin disrupting drug cytochalasin D and found that the wavelength of buckling increased. They also established that lateral support could produce shorter wavelength buckling in a macroscopic model system. In this experiment, the authors compared the buckling of a plastic rod imersed in water with one embedded in gelatin. Consistent with their theory, the gelatin matrix provided lateral reinforcement that shortened the buckling wavelength. Once buckling had occurred, all subsequent buckling occurred in the same local span along the rod. The implication is that the gelatin was weakened around the buckling region. Similarly, the authors found that buckling occurred repeatedly in the same locations as cardiac myocytes underwent cycles of contraction. Thus, like the gelatin, the cytoskeletal network supporting microtubules in cytoplasm might be mechanically heterogeneous, and regions lacking support are most likely to experience short wavelength buckling.

By extending classic column buckling theory to include the effects of a supporting gel-like medium, Brangwynne et al. [3] calculated that the forces required to buckle microtubules with such short wavelengths are greater than 100 pN. Because this force is much larger than could be generated by polymerization, they concluded that there must be a different, more potent source for microtubule compression. Consistent with repeated local buckling in cardiac myocytes, the authors argue that microtubule compression in the interphase cytoplasm develops in response to myosin-generated

tension. In this view, contractile tension is balanced by the resistance of focal adhesions on the outside of the cell and microtubule compression on the inside. The concept is consistent with the idea of cells as tensegrity structures [6] where gel-reinforced microtubule struts support myosin-based tension throughout the cytoplasm. The actin cytoskeleton plays a role both as the myosin substrate that compresses the microtubule, and as part of the mechanical network that protects the microtubule from structural failure.

While the observations of Brangwynne et al. [3] indicate that high tensile stresses and a gel-like mechanical environment exist throughout the cytoplasm of interphase cells, they also suggest a very different mechanical environment in settings where microtubules act as long-distance centering systems. For example, fission yeast use microtubules to center a nucleus even as the rod-like cells grow asymmetrically from one end. Experiments by Daga et al. [7], recently reported in *Current Biology*, show that plus-end microtubule polymerization is responsible for centering displaced nuclei. The growing microtubules push against the cell periphery with their growing ends and against the nuclear envelope on their other end. The compression generated between these surfaces causes microtubules to buckle with a long wavelength (Figure 1). Similar buckling shapes and mechanics are likely during eukaryotic mitosis when microtubule polymerization and motors position chromosomes and centrioles in the mitotic spindle [8]. Thus in these contexts, long wavelength buckling suggests low forces and little lateral reinforcement by other elements of the cytoskeleton.

It is intriguing to consider that microtubule buckling shapes might be routinely used as indicators of local mechanics in the cytoplasm; however, there are reasons to be cautious with this approach. Because some microtubule associated proteins bind to their sides to reinforce them mechanically [9], the mechanics of
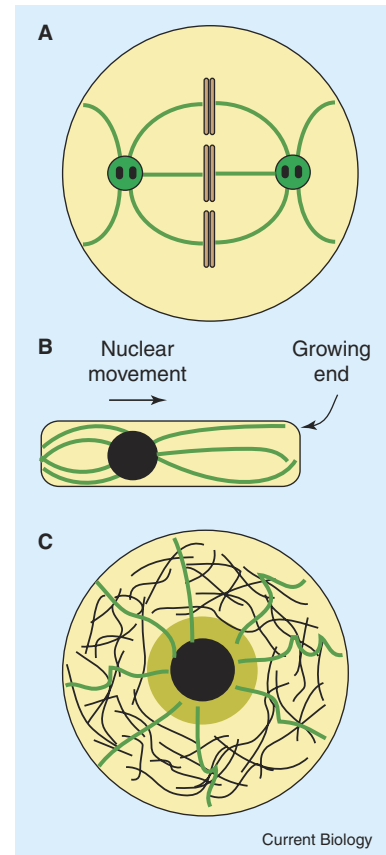

Figure 1. The different shapes of microtubules under pressure.

Microtubules experience compressive forces that cause them to buckle. When centering chromosomes in the mitotic spindle (A) or centering the nucleus of an asymmetrically growing fission yeast (B), microtubules are compressed by the forces of polymerization and buckle with long wavelength shapes. In the cytoplasm of interphase cells (C) microtubules occasionally experience more dramatic folds over local spans. New research suggests these short wavelength buckles are evidence of significant myosin-generated compression in the cytoplasm, and that interphase microtubules are likely to be laterally reinforced by their connections to actin and intermediate filaments.

individual microtubules may vary with nucleotide state [10], and structural defects can occur within microtubules [10], short range buckling may occur in regions of microtubules that are intrinsically weak [9], rather than in regions that are poorly reinforced. For these reasons, more should be done to test the conclusions of Brangwynne et al. [3]. One challenging, but feasible idea would be to correlate the locations of microtubule buckling

with the random movements of intracellular particle probes [11,12] to confirm that buckling occurs in pockets of weakened cytoskeleton.

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Naturalizing Cognition: The Integration of Cognitive Science and Biology

Descartes drove a wedge between human cognition and biology. Cognitive neuroscience is beginning to bridge the gap, and the application of mirror neuron theory to a range of problems in psychology has demonstrated the possibility of developing an understanding that spans from neural anatomy to language and empathy.

Arthur M. Glenberg

When Descartes reasoned from "cogito ergo sum" he allowed for progress in biology by divorcing it from church-controlled thinking about human psychology. Descartes' division was taken up by influential cognitive scientists who forged a psychology based on the computer metaphor: Thinking, it was proposed, is the manipulation of symbols by rules [1]. The symbols were stripped of all perceptual and motor content, thus becoming amodal, abstract and, importantly, implementable on computers. The claim became that, if a computer could be programmed to implement the correct algorithms, then the computer would not just be simulating thinking, it would be doing thinking. Although there have been strong objections to this claim [2], the elegant theorizing, the empirical successes and the apparent gap between body and mind forged a Cartesian program which has been generally adopted by the field of cognitive science. Recent findings [3,4], reported in this issue of *Current Biology*, which demonstrate the likely role of mirror neuron systems in language and social interaction, provide an alternative to Cartesian dualism and a natural science account of cognition.

The tremendous growth of cognitive neuroscience in the last two decades, fueled by the increasing availability of brain imaging technologies, began to bridge the gap between body and mind by demonstrating that coherent brain activity could be correlated with both simple and complex cognitive activity. But the proper explanation of those correlations remained elusive, in part because the images were interpreted in the context of Cartesian cognitive theories that did not reach down to the neural mechanisms. The discovery of mirror neurons helps to bridge the gap between cognition and biology by providing a neural mechanism that reaches up to psychological theory and suggests solutions to a range of problems in cognitive science [5,6].

Mirror neurons were first identified in area F5 of the macaque pre-motor cortex by single-cell recording. These neurons fire both when the animal engages in particular actions, such as grasping a peanut, and when the animal observes the experimenter grasp the peanut in a similar manner. Many of these neurons are specific to the type of grasp, such as a precision grip or a power grip, as well as the intent of the grip, for example, to place or to eat. Furthermore, the same neuron may also respond to the sound of the action, such as the sound of breaking open a peanut. Additional research has identified mirror neurons in the inferior parietal lobule [7].

The existence of mirror neurons strongly suggests a motor resonance mechanism for action recognition and understanding. That is, using the mirror neuron mechanism, animal A understands animal B's action and intent as the same action and intent that it would have in this situation [7]. Recognizing the intent of conspecifics would seem to be a prerequisite for sophisticated social organization, allowing learning from imitation and