environment in order to justify the Bayesian approach to human perception.

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# Mitosis: Taking the Measure of Spindle Length

**Recent studies have investigated the mechanisms responsible for setting spindle length — and how spindle length changes over the course of development.**

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You started life as a single fertilized egg and, after multiple divisions, the number of cells in your body is now one hundred times larger than the number of stars in the galaxy. The DNA in your cells originated from that first cell, propagated through rounds of duplication and segregation. This division of your genetic material continues to occur inside you about ten million times per second. An error could give rise to a cancer that will kill you. How can one cellular structure, the mitotic spindle, so accurately partition DNA in your various cells and tissues? A partial answer is that the premise of the question is wrong: it's not that one spindle functions repeatedly, rather the spindles in your different cells are different. Despite the biological and medical importance of the regulation of spindle form and function during development, we know very little about this phenomenon, and even less about the underlying processes responsible for it. In a recent issue of *Current Biology*, Greenan *et al.* [1] present a study of the mechanistic basis of the variation in spindle length observed during *Caenorhabditis elegans* embryogenesis. Work such as this should help to reveal how DNA can be correctly segregated in cells with different dimensions, morphologies, and environments.

All mitotic spindles are bipolar structures composed of cytoskeletal polymers called microtubules [2]. Microtubules in spindles are highly dynamic; they typically turnover with a lifetime of tens of seconds. The continual balance of polymerization, depolymerization, and new nucleation allows spindles to last orders of magnitude longer than the microtubules that they are made of. Microtubules that contact chromosomes on special regions, called kinetochores, become preferentially stabilized. These kinetochore microtubules are responsible for exerting the forces on chromosomes that result in their division. In addition to segregating chromosomes, the spindle partitions other cellular components, such as centrioles, which form the base of cilia during interphase. In mitosis, centrioles are incorporated into centrosomes, microtubule nucleating centers located at the spindle poles. While components of spindles have been studied in detail, we still do not know how these constituents work together to form spindles.

Many models of spindle organization have been devised. These can roughly be divided into two classes: mechanical models and dynamical models. Mechanical models propose that spindle morphology and size result solely from a balance of forces, with pushing by some factors, such as motor proteins and polymerizing microtubules [3], counteracted by resistance from other elements, such as opposing motors, microtubule rigidity [4], or chromosome stiffness [5]. These mechanical models are reminiscent of elasticity theory of simple physical structures like soap bubbles, whose shape is governed by a balance of surface tension and internal pressure. Dynamical models posit that spindle structure arises from the self-organization of the spontaneous activity of the constituent microtubules, motor proteins, and regulatory factors. Examples of dynamical models include the suggestion that spindle length is set by proteins that induce a length-dependent microtubule depolymerization [6], or the distance a microtubule slides during its lifetime [7].

An influential class of dynamical models is that spindle structure is

patterned by diffusible molecules that produce spatial gradients in the activity of proteins. Such reaction-diffusion mechanisms have been invoked to explain biological pattern formation in a wide variety of systems, ranging from organ development to subcellular signaling. In the spindle, gradients are thought to emanate from chromosomes and control microtubule assembly [8]. Other hypothetical gradients have been proposed to originate from the spindle midzone [9], centromeres [10], and kinetochore microtubules [11]. While the importance of various signaling pathways has been firmly established, it is very difficult to demonstrate that gradients of these regulatory molecules provide spatial information that is used in spindle formation or function.

In the new work, Greenan *et al.* [1] provide evidence for another gradient in spindles, this one emanating from centrosomes. The authors argue that the length scale of this gradient — of the protein TPXL-1 — sets the length of the mitotic spindle and that changes in the gradient give rise to the changes in spindle length that occur during *C. elegans* embryogenesis. Remarkably, Greenan *et al.* [1] suggest that the length scale of the TPXL-1 gradient is determined by the size of the centrosome. Support for this comes from the natural decrease in centrosome size that occurs during early embryonic divisions and RNAi experiments, including the amazing result that in spindles with two centrosomes of different sizes each half spindle has a different length [12]. It is still unclear how centrosome size might influence the decay of the TPXL-1 gradient and how this gradient might actually influence the length of the spindle.

Greenan *et al.*'s [1] gradient model for the changing length of the spindle in *C. elegans* development is very different from a mechanical model of the same phenomenon recently proposed by Hara and Kimura [13]. Perhaps there are elements of truth in both the mechanical and dynamical models of spindle length regulation in *C. elegans*? Or future work might show that one of these mechanisms is dominant. It will also be interesting to know if similar processes cause the decrease in spindle length during the development of other organisms [14] and the differences in spindle lengths between related species [15]. More broadly, while the mechanisms that determine spindle length are intrinsically fascinating, it is still unclear if the exact length of the spindle is really biologically important. After all, the changing length of the spindle during development demonstrates that spindles of different sizes can accurately partition the same genome and we should not assume that every observed cellular and developmental feature is adaptive [16]. The study by Greenan *et al.* [1] is an exciting step forward in understanding what cellular processes are modified during the course of development, but much work remains in this young and challenging field.

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# Neuronal Guidance: A Redox Signal Involving Mical

**Mical, a redox enzyme, binds the cytoplasmic domain of the semaphorin receptor plexin A and mediates semaphorin-signaled collapse of the actin cytoskeleton. Recent work now shows that Mical's ability to bind actin filaments and destabilize them in a NADPH-dependent manner is responsible for semaphorin 1a's effects.**

**Barbara W. Bernstein* and James R. Bamburg**

Mical proteins are a recently identified family of large (118 kDa), cytoplasmic, multidomain, actin-binding proteins [1], named for their molecular interaction with CasL, an adapter protein involved in cell adhesion. The surprising mechanism by which they fulfill their essential role in mediating axon guidance has been described by the Terman laboratory in a recent issue of *Nature* [2]. These studies clearly demonstrate that Micals have the unique capability of enzymatically promoting actin filament destabilization through a specific