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From cytoskeletal assemblies to living materials

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Many subcellular structures contain large numbers of cytoskeletal filaments. Such assemblies underlie much of cell division, motility, signaling, metabolism, and growth. Thus, understanding cell biology requires understanding the properties of networks of cytoskeletal filaments. While there are well established disciplines in biology dedicated to studying isolated proteins — their structure (Structural Biology) and behaviors (Biochemistry) — it is much less clear how to investigate, or even just describe, the structure and behaviors of collections of cytoskeletal filaments. One approach is to use methodologies from Mechanics and Soft Condensed Matter Physics, which have been phenomenally successful in the domains where they have been traditionally applied. From this perspective, collections of cytoskeletal filaments are viewed as materials, albeit very complex, 'active' materials, composed of molecules which use chemical energy to perform mechanical work. A major challenge is to relate these material level properties to the behaviors of the molecular constituents. Here we discuss this materials perspective and review recent work bridging molecular and network scale properties of the cytoskeleton, focusing on the organization of microtubules by dynein as an illustrative example.

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Introduction

Treating the cytoskeleton as a material provides a powerful framework to understand cellular-scale phenomena such as the structure of the spindle [1], the dynamics of the cell cortex [2], and the flickering behavior of red blood cell membranes [3]. The benefits of the material approach come at a price: the system is described at large scales, with only coarse reference to the underlying molecules. In cell biology, we would ultimately like to determine how molecular processes give rise to cellular phenomena. This will require understanding how the coarse-grained, material properties of collections of cytoskeletal filaments emerge from the properties of the individual proteins of which they are composed.

In this review, we discuss a path to bridge molecular and coarse-grained properties of the cytoskeleton based on ideas adapted from the statistical mechanics of materials. To illustrate, we emphasize recent work which suggests that the role of dynein in spindle assembly is to generate a contractile isotropic active stress due to dynein clustering of microtubule minus-ends. We outline a theory that connects the large-scale behaviors of networks of microtubules and dynein, to the manner in which dynein slides pairs of microtubules relative to each other. We compare and contrast this with other cytoskeletal systems that exhibit different behaviors on molecular and cellular scales.

Dynein in spindles, extracts, and purified systems

Dynein is a minus-end directed molecular motor that is believed to associate with microtubule minus-ends in spindles because: first, it is enriched near spindle poles [4,5], where microtubule minus-ends are also enriched [6]; second, dynein rapidly accumulates at microtubule minus-ends that are newly generated when spindle microtubules are severed [7]; third, stabilized microtubules in mitotic and meiotic cell extracts can organize into asters in a dynein-dependent fashion, with both dynein and microtubule minus-ends at the aster core [8,9]. Dynein plays a major role in spindle assembly, as evidenced by inhibition and depletion/knockdown experiments, which result in elongated, barrel-shaped spindles without focused poles [10–13]. Thus, dynein contributes to the formation of spindle poles, but how, exactly?

We recently investigated the role of microtubule motors in the complex environment of *Xenopus* egg extracts [14,15•], which contain all components necessary for spindle assembly [10]. Adding taxol to these extracts caused microtubules to be nucleated and stabilized. The resulting microtubules formed a macroscopic network that spontaneously contracted. Inhibition

experiments showed that the network contraction is primarily due to the activity of dynein. Thus, dynein drives network contractions in *Xenopus* egg extracts.

Dynein's ability to organize microtubules has been further investigated in simplified reconstituted systems. A purified active form of the dynein complex has been shown to accumulate on microtubule minus-ends *in vitro* [16], consistent with the putative localization of dynein on the minus-ends of spindle microtubules. The minus-end localized dynein can cross-link pairs of microtubules, causing their minus-ends to slide together, irrespective of filament's relative orientation [17•]. This behavior is quite different from other molecular motors such as Kinesin-5 [18] and Kinesin-14 [19], which bind pairs of microtubules along their length and preferentially slide apart anti-parallel, but not parallel, microtubules. At higher concentrations, purified mixtures of activated dynein and stabilized microtubules organize into contractile networks [17•], which are remarkably similar to those structures in *Xenopus* egg extracts [14]. Thus, dynein drives network contractions in *Xenopus* egg extracts, and it is sufficient to produce microtubule network contractions in purified systems, but how?

As detailed below, a theory containing the observed minus-end clustering activity of dynein is sufficient to produce contractile stresses that can quantitatively explain diverse aspects of the behavior of the contractile microtubule networks. We conjecture that these same contractile stresses, driven by minus-end clustering, may explain how dynein drives spindle fusion [11] and the role of dynein in spindle pole formation.

Related systems

It has been argued that motor-induced end clustering is a generic mechanism to produce contractions of cytoskeletal networks [20,21••,22]. Indeed, Kinesin-14 and Kinesin-5 can both organize purified microtubules into asters, which presumably form from end-clustering, and, at higher microtubule concentrations these systems can form contractile networks [19,23,24]. It thus seems plausible that these network contractions are also driven by end-clustering. Furthermore, recent work demonstrated that myosin can accumulate on the ends of actin filaments, and cluster those filament ends together [25], arguing that contraction of actin networks might be driven by this same process. Thus, contractions of actin networks and microtubules networks might ultimately result from similar processes.

In addition to forming contractile networks, purified systems of microtubules and motors, and purified systems of actin and motors, can both form aligned, flowing states [26,27]. The microtubule and actin aligned systems show similar emergent phenomena: the continual creation and annihilation of topological defects and the spontaneous motility of defects. One key difference between these flowing, aligned systems and the contractile, isotropic systems is the presence of depletants, which causes a short-range attraction between filaments, that drives them into the aligned state. Intriguingly, without depletant, the same Kinesin clusters used in [26] instead organize microtubules into asters and vortices [28]. Thus, changing network composition can lead to large changes in network behaviors [29]. Understanding how and why these different bulk behaviors emerge from molecular-scale interactions is an open question.

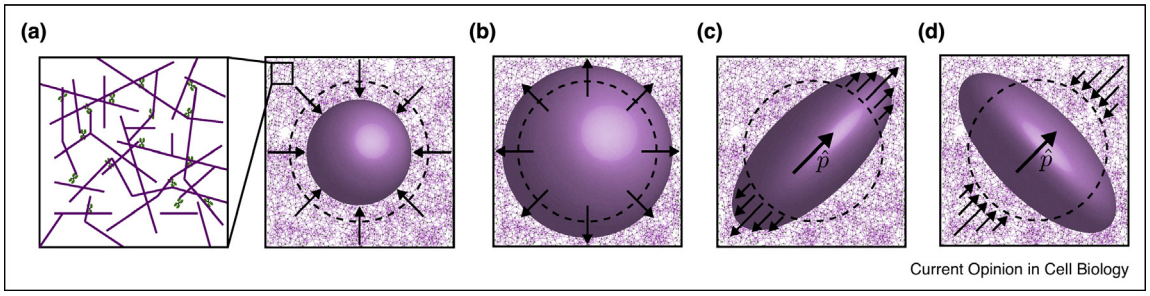
The material science of living systems

In order to connect the molecular and cellular scale properties of cytoskeletal networks, one needs a framework to describe the large length-scale behaviors of these systems. One approach is to model cytoskeletal networks as soft continuum materials. Historically, this begins with Euler's formulation, in 1757, of fluid flow as partial differential equations expressing mass and momentum conservation. This was generalized by Cauchy who introduced the stress tensor as the fundamental object of modeling. Statistical physics has since sought to establish how such macroscopic continuum descriptions arise from the interactions of a material's microscopic constituents. Continuum ideas are proving fruitful in describing active biological matter. What are the key ideas?

The first is the *Continuum Hypothesis*. Its essence is to assume that there are so many microtubules in our system that their dynamics are faithfully represented by continuous fields in space, such as their (number) density, $\rho(\mathbf{x}, t)$, and a velocity field, $\mathbf{v}(\mathbf{x}, t)$. To construct such continuous objects one needs *scale separation*, for example, if L is the system size, and L_{MT} a typical microtubule length, there is an intermediate scale, L_{avg}, such that L_{avg} is small compared to the system size L but large compared to the length of a microtubule L_{MT}, over which discrete properties can be averaged to yield continuous fields (see Figure 1a). ρ and $\mathbf{v}$ are connected by the *continuity equation*, a fundamental differential relation that says that a net flow of material into a region tends to cause an increase in density, while a net flow out of a region causes a decrease in density.

Motions, that is the velocity field $\mathbf{v}(\mathbf{x}, t)$, are generated by forces. A central task is to understand the forces that a material exerts upon itself. One complication is that materials can exert different forces in different directions. Cauchy showed that this feature was mathematically described by the *stress tensor*, which is a 3×3 tensor (or matrix) $\boldsymbol{\Sigma}(\mathbf{x}, t)$. This makes some sense as matrices, through multiplication, transform vectors (here a direction) to vectors (here a force per unit area, or stress vector). The tensor field $\boldsymbol{\Sigma}(\mathbf{x}, t)$ represents both the internal active forces (from motors) that drive motion, and the passive

Figure 1



An illustration of different types of contractile and extensile stress fields. **(a)** The left panel represents a magnified averaging volume used to define continuous fields of density, velocity, and other quantities across the larger sample in the right panel. This panel also illustrates the isotropic, contractile stress vector field generated by the stress tensor $\boldsymbol{\Sigma} = -\alpha\mathbf{I}$ where $\alpha > 0$. Here the stress vector field is that exerted upon a sphere of material (dashed curve) by the surrounding material leading to its volumetric compression. **(b)** The isotropic, extensile stress vector field produced by setting α negative. **C** The extensile, *dipolar* stress vector field generated by the 'rank-one' stress tensor $\boldsymbol{\Sigma} = \beta\mathbf{p}\mathbf{p}^T$, where $|\mathbf{p}| = 1$ and $\beta > 0$. Here a sphere of material is extended along the **p** direction. **D** In the contractile version where $\beta < 0$, the sphere is compressed along the **p** direction.

forces (like microtubule collisions or cross-linkers) that resist them.

For example, let us say a stress tensor $\boldsymbol{\Sigma}^a$ models the internal active forces that drive material rearrangements. Figure 1a shows the *isotropic*, *contractile* stresses (forces per unit area) in a material arising from the simple stress tensor $\boldsymbol{\Sigma}^a = -\alpha\mathbf{I}$ where $\alpha > 0$ and $\mathbf{I}$ is the identity tensor. This type of stress appears when modeling how the clustering of microtubule minus-ends by dynein drives network contractions [14]. In addition to isotropic stresses that cause changes in volume, motor induced active stresses can also have anisotropic, or 'dipolar', structure as illustrated by Figure 1c and d. This stress form arises when modeling how polarity-sorting by motors lead to extension of bundles [20,30,31], and is responsible for the spontaneous flows in aligned systems of microtubules or actin [26,27]. Active stresses can be resisted by a viscous response of the material to being sheared or strained, or by elastic deformation of filaments or cross-links. These stresses can also be represented through stress tensors that capture these responses. An added complication can be that these materials are immersed in a fluid (say, cytoplasm) which can modify the material motions both by exerting drag and by facilitating long-range interactions [30].

Another important concept in describing complex materials is that of *order parameters*. For example, a tensor-valued order parameter, commonly called $\mathbf{Q}$, naturally describes the *orientational order* of a microtubule assembly, expressing how well, and in what direction, microtubules are mutually aligned. The tensor $\mathbf{Q}$ again appears naturally when modeling the material stresses that depend upon the local arrangement of microtubules [31,30]. Indeed, order parameters are central to formulating stresses and must be evolved using dynamical equations based upon physical modeling. Note that even in the absence of local order, active stresses can exist and drive material motion [14]. If inertial forces are negligible, and no external forces act on the system, then all of the forces generated by internal stress fields add up to zero. This establishes a relation between active stresses and the passive stresses, and is typically the relation that determines the material velocity $\mathbf{v}$ that moves the material, changes the density, and evolves other fields.

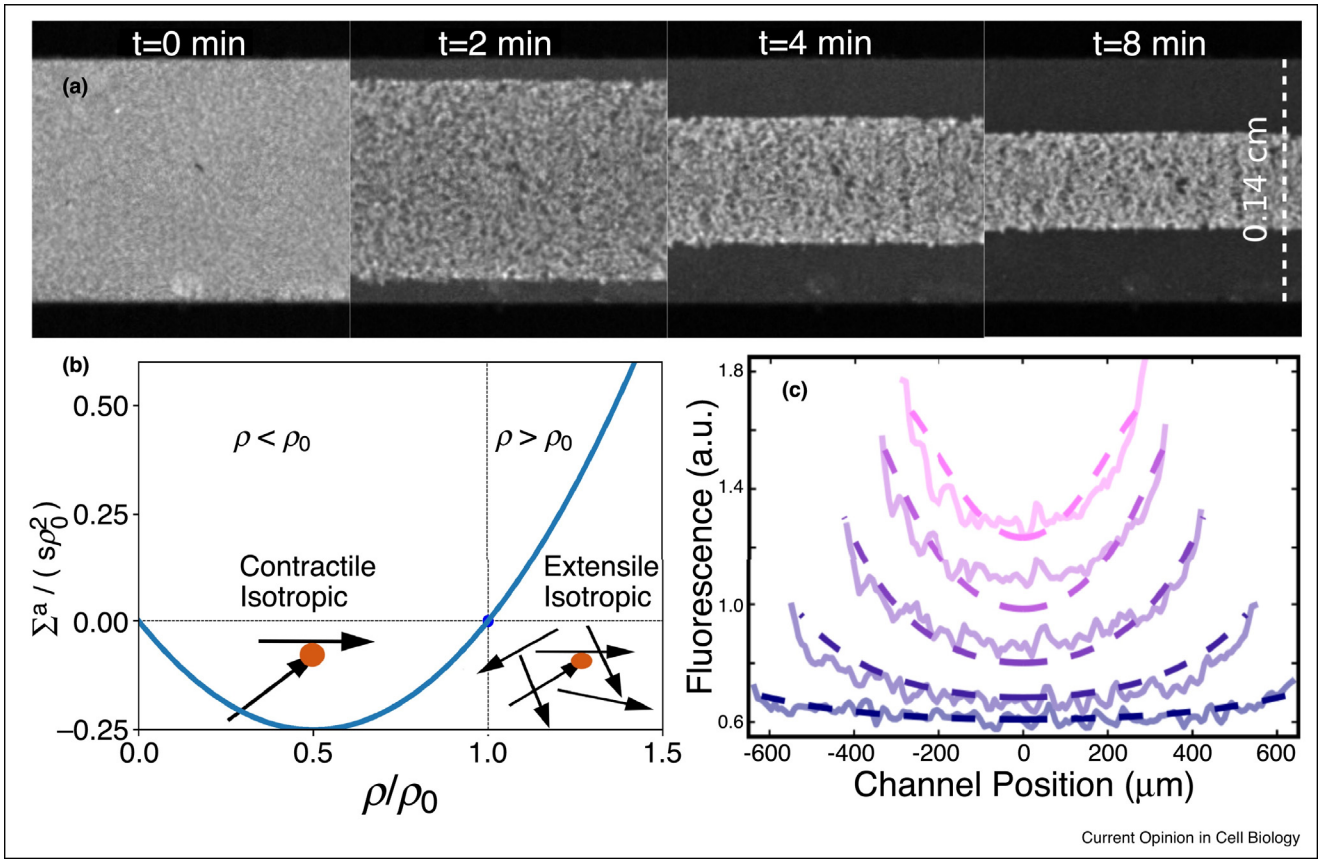
From molecules to materials

Given these notions of continuous density, velocity, stress, and order fields at macroscopic scales, how are their evolution — and thus their emergent properties — determined by the interactions of their microscopic constituents? One route has been to extend methods from the physics of interacting particle systems [32] to incorporate the active processes which drive biological systems. We take up the example of contractile microtubule networks (see Figure 2a) which, to make sense of experimental observations, we modeled as a continuous material [14].

In this theory we model the motion of the minus-ends of microtubules, and assume that the orientations of microtubules are completely random because of the apparent disorder of the networks.

Invoking scale separation, assume there is a small cube of volume $V_{avg} = L_{avg}^3$, centered at a point $\mathbf{x}$ in the experimental volume, and in which we have many microtubules. If the box has N microtubules in it, we define the density $\rho = N/V_{avg}$. The material velocity $\mathbf{v}$ is simply the average velocity of all the minus-ends within the cube. These two (hopefully) smooth fields will then satisfy the continuity equation mentioned in the last section.

Figure 2



A system of taxol stabilized microtubules in *Xenopus* extract spontaneously contracts **(a)**. Our modelling predicts a stress $\Sigma^a = -s\rho[\rho_0 - \rho]\mathbf{I}$, shown in **(b)**, which incorporates the effects dynein driven motor minus end clustering (contractile) and steric interactions (extensile), which balance at the intrinsic density $\rho = \rho_0$. **(c)** A model based on this stress yields good agreement between experimental contractions and theoretically predicted ones. We display the density of material averaged along the long axis of the system and compare experimental results (solid lines) to theoretical predictions (dashed lines). The different shades of color in (C) denote subsequent time points (1min intervals). Figure adapted from [14].

How do the minus-ends interact? Having isolated dynein as the driver of contraction, and having the idea that dynein clusters minus-ends together, we assume that if two minus-ends are sufficiently close, they can be pulled together by an end-attached dynein. Resisting this contraction is the steric repulsion arising from microtubules colliding with each other. For both attraction and repulsion, all forces arrive in equal and opposite pairs, as required by Newton's Third Law. Each force pair (force dipole) in the material generates a stress in the material that is proportional to the force and the displacement between the application points of the force. Averaging these stresslets over a local volume element is encoded in the Kirkwood Formula of interacting particle systems [32] and gives the volume-averaged stress. In the case of having a limited number of motors and small interaction distances, this yields a density dependent *active isotropic stress* $\boldsymbol{\Sigma}^a$ that is the sum of motor-induced contractile stress and sterically induced extensile stress, see Figure 2b. At a special density, $\rho = \rho_0$, the effects of dynein induced clustering and steric interactions exactly balance, so the total active stress is $\boldsymbol{\Sigma}^a = 0$. If $\rho < \rho_0$ the active stress is isotropic contractile (see Figure 1a) and transitions to isotropic extensile (see Figure 1b) for $\rho > \rho_0$.

The active stress acts against the material's tendency to resist deformations, which we model to be proportional to the rate at which the material deforms (viscous stress) and against the drag force between the microtubules and the background fluid. The balance of the viscous stresses, active stresses and the drag force, yields an expression for $\mathbf{v}$, the velocity of the material, as a function of the material density. This continuum material description recapitulates the dynamics of the contracting microtubule network very well (Figure 2c), and also explains how the time-scale of contraction varies with the size of the network and that inhibiting dynein influences the speed

of contraction, but not the final density the network contracts to [14].

Our theory can be extended to incorporate local ordering, which dominates in many other systems, by using ideas from *active suspension* theories. In these theories, the crosslinked cluster of molecular motors and cytoskeletal filaments exerts an active stress on the fluid which surrounds it. This in turn generates fluid flows which couple the dynamics of active elements over length scales much larger than individual microtubules. The microscopic physics of motors and filaments enters through the stress which each active element exerts.

While originally developed for bacterial suspensions [33–35], the *active suspension* approach has proven flexible enough to accommodate much of the essential physics of extensile microtubule suspensions [30] using parameters derived from interactions between molecular scale motors and microtubules. In parallel, other groups [36–38] followed Boltzmann's idea of encoding the interactions between filaments in terms of a binary collision kernel, and Smoluchowski's approach of encoding microscopic interactions in terms of flux balances [39–41]. While different in some aspects [42] a commonality between all these theories is that they strictly apply only when the filaments are dilute. Many cell biological systems of interests form highly cross-linked networks. There is increasing evidence that such dense networks might have important differences from dilute systems [43,44•]. In [21•] the authors predict the initial contraction behavior of a highly percolated network from the properties of the network's motor proteins and crosslinkers. Building a continuum material along these ideas is an open challenge.

Conclusion

While still a nascent approach, taking this material science perspective has already had some successes in understanding biological phenomenon. For example, the actin cortex of *C. elegans* embryos was shown to behave as an active chiral fluid, where the chiral flows emerge from active forces and torques generated by actin and myosin [2]. These chiral flows break left-right symmetry in the embryo, and ultimately help to establish the body axes during development. The organization and dynamics of spindles formed in *Xenopus laevis* extracts have also been shown to be well described using an active liquid crystal theory, and the theory's phenomenological parameters have been measured [1]. This same theory is sufficient to explain the morphology of the spindle. Connecting the parameters of these theories with the molecular-scale interactions is a future challenge.

Conflict of interest

Nothing declared.

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