Active matter at the interface between materials science and cell biology

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Abstract | The remarkable processes that characterize living organisms, such as motility, self-healing and reproduction, are fuelled by a continuous injection of energy at the microscale. The field of active matter focuses on understanding how the collective behaviours of internally driven components can give rise to these biological phenomena, while also striving to produce synthetic materials composed of active energy-consuming components. The synergistic approach of studying active matter in both living cells and reconstituted systems assembled from biochemical building blocks has the potential to transform our understanding of both cell biology and materials science. This methodology can provide insight into the fundamental principles that govern the dynamical behaviours of self-organizing subcellular structures, and can lead to the design of artificial materials and machines that operate away from equilibrium and can thus attain life-like properties. In this Review, we focus on active materials made of cytoskeletal components, highlighting the role of active stresses and how they drive self-organization of both cellular structures and macroscale materials, which are machines powered by nanomachines.

"I define the Organism, or natural Machine, a machine in which each part is a machine […], whereas the parts of our artificial machines are not machines" (REF. 1). This statement made by Gottfried Wilhelm Leibniz in 1704 points out a key difference between living and non-living entities that is still true today. The Merriam-Webster dictionary defines a machine as "an assemblage of parts that transmit forces, motion, and energy one to another in a predetermined manner". Thus, all machines are intrinsically non-equilibrium systems and require a continuous input of energy. A prototypical artificial machine of the 20th century, the internal combustion engine, uses chemical fuel to operate far from equilibrium but is entirely assembled from ordinary, 'dead', metal components. Living organisms also require chemical energy to fuel diverse chemo-mechanical processes, but these are simultaneously carried out at multiple, hierarchical levels (FIG. 1), and each individual part is internally driven. At the most basic level, protein-based molecular machinery undergoes conformational changes that lead to motility, force generation and chemical reactions. Together with various associated proteins, these elemental machines self-organize into higher-order subcellular structures, such as the nucleus, the Golgi apparatus and the mitotic spindle. In turn, these active subcellular structures are the basic building blocks of biological cells. At even higher levels, biological cells self-organize into complex energy-consuming tissues and entire organisms. Each level of hierarchical organization is associated with the emergence of entirely new behaviours, which can only arise in non-equilibrium environments.

The realization that the collective dynamics of energy-transducing molecules underlies many biological phenomena leads to the question of how, in general, such systems behave. In particular, it is interesting to investigate which types of structures they can form, which kinds of dynamics they can display and, given a particular set of microscopic elementary units, what range of possible macroscopic architectures, patterns and functionalities can be realized. Whereas equilibrium statistical mechanics predicts the behaviour of 'dead' materials, there is no analogous theory for non-equilibrium self-organized hierarchical systems of active matter. The field of active matter is concerned with non-equilibrium systems in which the individual, constitutive units are themselves internally driven: machines made from machines. Its goal is to elucidate fundamental principles that underlie the emergence of large-scale patterns and behaviours in these systems.

Active matter is different from traditionally studied non-equilibrium phenomena such as Rayleigh–Bénard convection[2] (observed in a layer of fluid heated from below, which develops a regular pattern of convection cells): intricate Rayleigh–Bénard patterns are non-equilibrium

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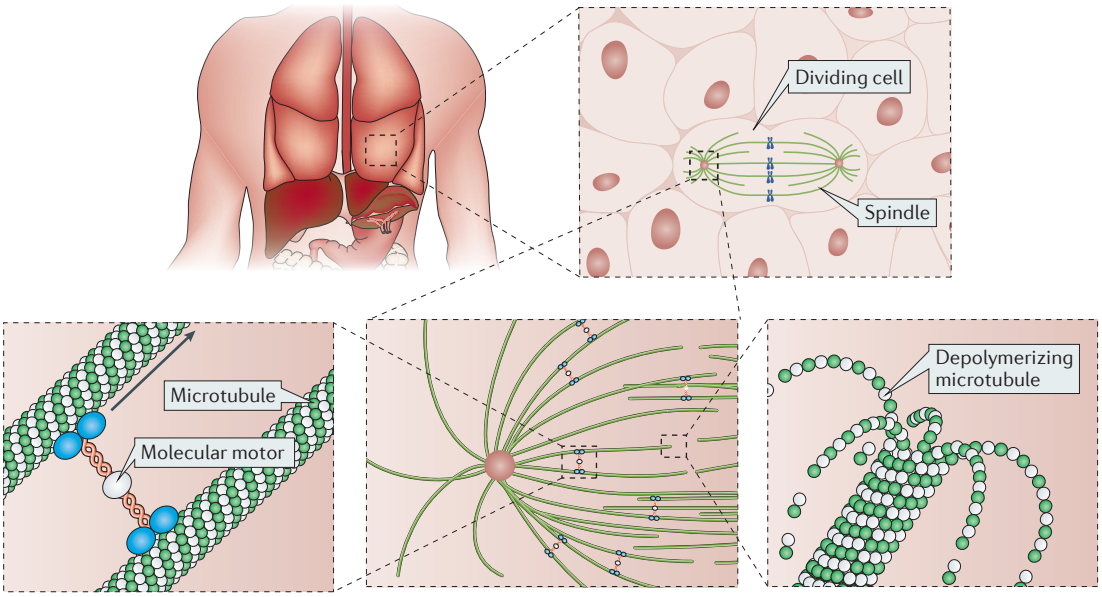

Figure 1 | **Organisms are machines made from machines.** Organisms are composed of tissues, which are non-equilibrium assemblages of cells. Cells are built from non-equilibrium self-organized structures, and subcellular structures are composed of energy-transducing molecular motors and filaments. In the schematic, one cell is undergoing cell division and contains a spindle (a structure that segregates chromosomes during cell division), which is made of microtubules (filament structures in the cytoskeleton) and molecular motors. The close-up views show a molecular motor that is crosslinking and sliding between two microtubules and the end of a microtubule that is dynamically shrinking.

dissipative structures, but each convection roll is composed of passive molecules, and the entire system is driven away from equilibrium by energy provided through an external macroscopic boundary. By contrast, the cellular cytoskeleton, cells and entire tissues are driven away from equilibrium by the continuous motion of thousands of constituent nanoscale molecular motors, protein-based machines that transform chemical energy into mechanical motion[3,4]. Collectively, such microscopic activity leads to the emergence of new behaviours at each level of hierarchical self-organization, enabling the survival and reproduction of living organisms. In the absence of sufficient chemical fuel, these microscopic life-sustaining processes grind to a halt, leading to equilibrium and death.

The field of active matter lies at the interface between the physical and life sciences. Early foundational experiments used motile agents of biological origin to assemble bulk active materials[5,6]. These experiments, together with biological phenomena observed across many length scales, inspired the development of theoretical models of active matter[7–9]. Thus, biology stimulated the creation of a new research area in materials science. In return, the quantitative understanding of simplified *in vitro* systems has the potential to profoundly influence our understanding of complex self-organization in biological cells.

Here we review recent advances that have transformed active matter into a mature and rapidly expanding research field that spans diverse disciplines, ranging from soft matter physics to cell biology, to materials science, and to engineering. We focus on experimental work at the interface between cell biology and materials science, as well as on the potential for each of these lines of research to influence and benefit the others. We first provide a brief historical perspective on the importance of active processes in the biological organization of cells. Next, we discuss active materials assembled from purified cytoskeletal components, which are classified according to the symmetries of their structures and stresses, and we review advances that demonstrate the essential role of active stresses and out-of-equilibrium self-organization in cytoskeletal systems in cells. We conclude by placing these topics in the broader context of other realizations of active matter. We also note that active matter is a much broader field that is being investigated using a wide array of synthetic model systems that are either externally or internally driven. Other reviews have discussed recent advances from complementary perspectives[10–17].

Cell biological systems are active matter

Although attempts to determine the physical principles that account for cellular structures and behaviours date back a long time, the central importance of non-equilibrium self-organization has only recently been emphasized. Early efforts to understand the physical basis of life sought to explain biological phenomena observed under the microscope by referring to physical systems that could produce qualitatively similar patterns. Such work focused on trying to apply known physics to explain poorly understood biological processes. Around 1900, researchers used analogies with the mechanical bending of macroscopic beams to explain cytokinesis and simple electrostatics to explain mitosis, whereas in the 1930s ideas from physical chemistry, such as diffusion and osmotic stresses, were invoked to explain those phenomena[18,19]. Advances in biochemistry and electron

microscopy in the 1950s and 1960s revealed the highly intricate internal organization of cells, which were observed to contain ubiquitous polymeric and membranous structures, clearly demonstrating that apparent similarities between cell biological and simple physical systems were merely superficial[20]. It became evident that subsequent theories describing cellular structures and behaviours would need to be based on the increasingly sophisticated understanding of the structural composition of cells. In the 1970s, the idea that cellular structures assembled by minimizing the free energy of their subunits gained traction. This concept, called self-assembly, was posited to explain various structures including those of viruses, actin filaments and even the mitotic spindle[21,22]. Although the self-assembly theory was grounded in a basic understanding of the molecular constituents of cells, it still shared a fundamental assumption with previous physical theories of cellular organization: that the material inside cells is locally at equilibrium.

Many biological phenomena are clearly non-equilibrium in origin, and have long been recognized as such: examples include muscle contractions, cytoplasmic streaming and development[23]. The non-equilibrium nature of organisms has even been considered as one of the defining features of life[24]. Despite this, explicit theories of subcellular organization did not make extensive use of non-equilibrium concepts until the 1980s. The initial focus was on the implications of adenosine triphosphate (ATP) and guanosine triphosphate (GTP) hydrolysis during the assembly of actin and microtubules, which, it was realized, allowed filament nucleation and growth to be decoupled, giving rise to new principles for understanding cellular organization[25]. Subsequent work in the late 1980s and early 1990s revealed that motor proteins reorganize cytoskeletal filaments by crosslinking them and causing them to slide relative to each other[26–28]. The importance of energy consumption in filament polymerization dynamics and rearrangement by motor proteins led to the modern view that the cytoskeleton organization is predominantly determined by these non-equilibrium processes[29,30]. By the early 2000s, advances in live cell imaging and molecular cell biology demonstrated that many subcellular structures are highly dynamic assemblages composed of energy-consuming enzymes, making non-equilibrium self-organization the dominant paradigm for understanding much of cell biology, including the spindle, the nucleus and the Golgi apparatus[31–33]. The non-equilibrium nature of subcellular structures endows them with remarkable properties. For example, spindles can fuse with each other, self-heal and transform between different architectures (FIG. 2). Molecular motors and monomer turnover are essential for all these processes.

Bioinspired synthetic active matter

The essential role that self-organization has in cell biology suggests that the use of internally driven components is the key to building materials with functionalities that have so far been confined to living organisms. The remarkable and diverse properties of cells arise from a highly conserved and fairly limited set of microscopic components. Evolutionary processes constrain the number of self-organized structures found in living organisms as compared with the much vaster manifold of all possible dynamical states that can be assembled from the same set of building blocks. Systematically assembling biological materials from the bottom up allows exploration of the phase space of all possible dynamical states. Thus, *in vitro* studies not only have the potential for reproducing the properties and behaviours of biological materials found in living organisms, but also for uncovering entirely new phenomena that lack direct biological relevance. Such work does not just advance materials science; the simplified, well-controlled nature of *in vitro* systems allows detailed tests of principles of active matter, which, in turn, provides a rigorous foundation for understanding complex self-organizing processes taking place inside cells.

Synthetic active matter systems have been constructed from the components of the cytoskeleton, that is, filamentous polymers and their associated proteins. Similar to the cellular cytoskeleton, such synthetic materials are driven away from equilibrium by the two elementary energy-consuming processes that drive the cytoskeleton: ATP-fuelled stepping of molecular motors, and ATP-fuelled or GTP-fuelled cycles of polymerization and depolymerization. The two main filamentous structures found in the cytoskeleton are actin and microtubules. Both filaments are inherently polar; thus, molecular motors move towards a specific filament end. Myosin motors move along actin filaments, whereas kinesin and dynein motors walk along microtubules. Each category of motors is classified into further subcategories that depend on their evolutionary history. Motors can be either processive or non-processive[34,35]. Processive motors can take hundreds of successive steps before dissociating from a filamentous track, whereas non-processive motors take only a single step along a filament before unbinding.

Rapid advances in the study of cytoskeletal active matter have been fuelled by several seemingly disparate developments spanning diverse scientific fields. First, the emergence of techniques that measure single-molecule dynamics has revolutionized our understanding of how individual molecular motors transform chemical energy into mechanical motion[36–39]. Simultaneously, the development of molecular biotechnology has provided access to highly active molecular motors and associated proteins. These advances have enabled the assembly of bulk synthetic materials whose properties can be precisely tuned and thus used to test theoretical predictions. A factor that greatly aids comparison with theory is the high efficiency of cytoskeletal molecular machines, which enables the assembly of bulk 3D materials with dynamics that can persist for hours and even days. Over this time span, cytoskeletal active matter can attain its true steady-state dynamics. Other promising routes for the study of active matter, such as the possibility of engineering the microscopic dynamics of molecular motors[40–42], have not yet been fully exploited.

An important early study examined the behaviour of purified microtubules and clusters of kinesin molecular motors, which can simultaneously bind two microtubules

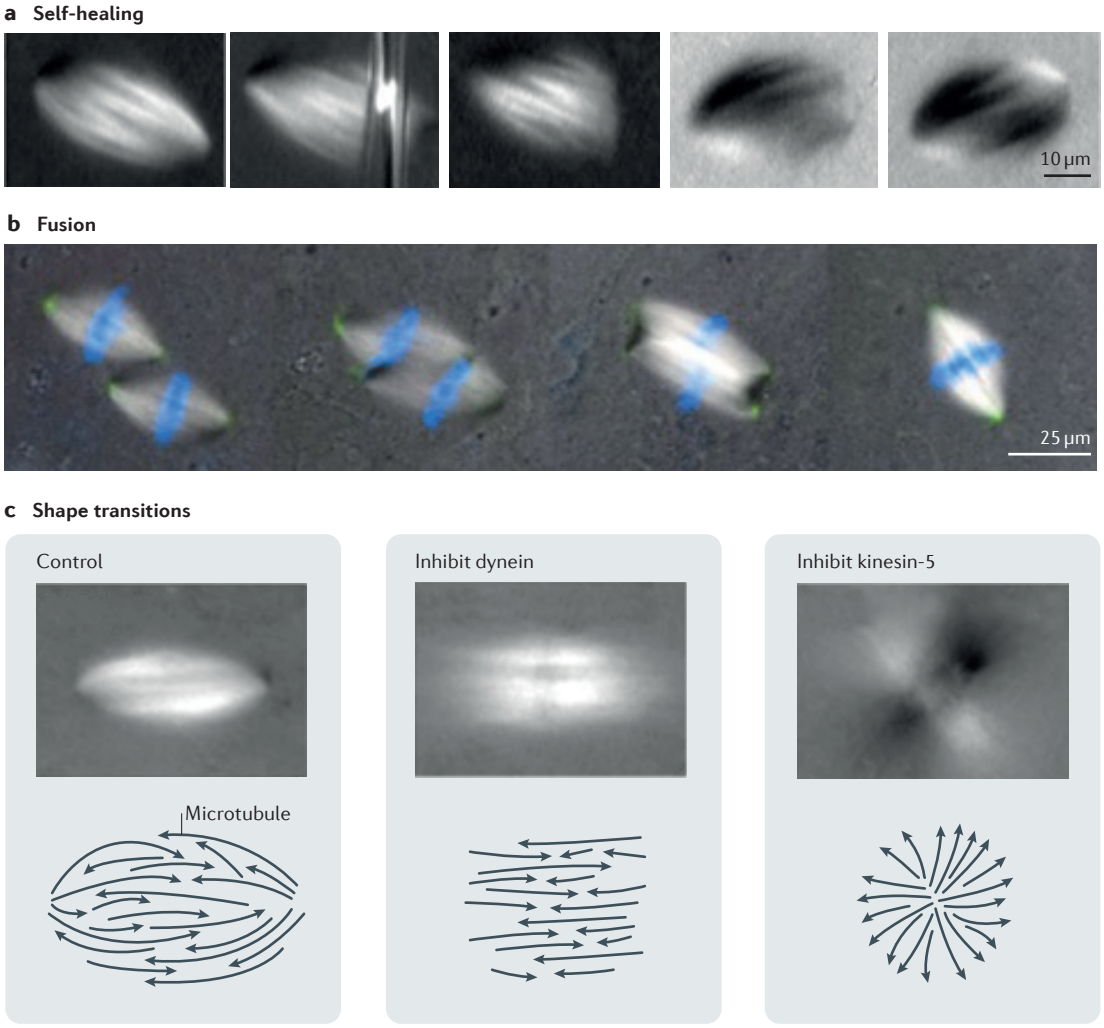

Figure 2 | **Properties of mitotic spindles.** Spindles are self-organized structures composed of microtubules, molecular motors and other associated proteins that segregate chromosomes during cell division. They exhibit highly dynamic non-equilibrium behaviours. **a** | Time-lapse images taken by polarized light microscopy, showing a spindle with a cut pole spontaneously healing itself[166]. The first image shows the intact spindle, the second the cutting of one of the poles; subsequent images show that the spindle is progressively reformed in a process that takes about 10 minutes. **b** | Two spindles brought into close proximity fuse to form a single spindle of similar size to the original spindles[167]. The blue and green regions in each spindle indicate the chromosomes and spindle poles (NuMa), respectively. **c** | The inhibition of different molecular motors (in these examples dynein and kinesin-5) causes the spindle to form different steady-state structures, as shown in the images and in the accompanying schematic depictions[168]. Panel **a** is republished with permission from REF. 166; permission conveyed through Copyright Clearance Center, Inc. Panel **b** is adapted with permission from REF. 167, Cell Press. Panel **c** is republished with permission from REF. 168; permission conveyed through Copyright Clearance Center, Inc.

and induce their relative sliding. Above a threshold concentration of microtubules, kinesin clusters generated distinct non-equilibrium patterns, depending on the biochemical properties of the kinesin motors[6]. In particular, kinesin-1 clusters induced the formation of radial aster-like structures, in which the motors and the plus ends of microtubules were concentrated in the centre of the aster, whereas the minus ends pointed radially outwards[5,43]. By contrast, clusters of non-processive ncd-kinesin motors, which walk towards the microtubule minus ends, induced the formation of vortices at intermediate microtubule concentrations and of asters at high concentrations; the asters were enriched in their centre with the microtubule minus ends[6]. Intriguingly, combining plus-end-directed and minus-end-directed motors led to a lattice of asters with cores alternatively enriched with plus and minus ends. Computer simulations suggested that the essential requirement for aster formation is the inherent tendency of motors to pause once they reach the microtubule end[6,44], but this prediction has not been experimentally tested. A better understanding of the structure and dynamics of molecular motors bound to filament ends would provide a more stringent test of these ideas. Furthermore, the factors that determine the structure, long-term stability and interactions of asters remain poorly understood.

Symmetries in active matter

Many additional studies of the self-organization of cytoskeletal filaments and molecular motors have been conducted, leading to the observation of a wide variety of behaviours. As in traditional condensed matter systems[45], in the classification of active matter systems it is helpful to focus on their symmetries, which determine their behaviours at large length and timescales and the type of topological defects they can host. Cytoskeletal filaments are polar objects, which can arrange to form systems with different symmetries (FIG. 3a). If the filaments are not oriented relative to each other, the assemblies they form are structurally isotropic at large length scales. These systems can be further classified as fluids or gels, depending on whether they are predominately liquid-like or solid-like, respectively. Collections of filaments that are positionally disordered but orientationally ordered form liquid crystalline phases. Nematic liquid crystals contain filaments that orient along a preferential axis and point in either direction along that axis, whereas polar liquid crystals contain filaments that point in a common direction. Topological defects (FIG. 3b) are singularities in the continuous field used to describe the order of a system. These defects are characterized by a topological charge; whether a topological defect is positively or negatively charged depends on the sense of rotation of the director field along a closed path encircling the defect. The magnitude of the defect charge is determined by the rotation of the orientation of the filaments along this path, with a rotation of π corresponding to defects with a charge of ±1/2. In nematic liquid crystals, the lowest-energy defects have a charge of ±1/2. The symmetries of polar liquid crystals do not allow defects of charge ±1/2; instead, they host defects with integer charge. Nematic liquid crystals can also form defects with integer charge; however, these have not been experimentally observed in liquid crystals formed from cytoskeletal filaments. Isotropic materials do not host topological defects.

Molecular motors continuously hydrolyse ATP to generate local forces as they move along and push and pull on cytoskeletal filaments. At length scales much bigger than the interatomic distances, such forces produce active stresses, which, along with the mechanical properties of the material, determine how volume elements deform and interact with each other. Similar to the structural properties, active stresses can have different symmetries (FIG. 4). Isotropic active stresses, such as conventional pressure, lead to uniform expansion or contraction. By contrast, dipolar active stresses lead to flows but not to changes in volume. They have no analogue in equilibrium systems and are responsible for many of the unusual properties of active matter. A system with an inherent tendency to extend along its nematic or polar axis is referred to as 'extensile' (in the dipolar sense), whereas a system which contracts along that axis is referred to as 'contractile' (again, in the dipolar sense). Confusingly, systems with isotropic contractile stresses are also called contractile, although isotropic contractility and dipolar contractility are different phenomena. We are not aware of any cytoskeletal system that has been demonstrated to be extensile in the isotropic sense. In the following, we discuss experimental studies of several systems composed of cytoskeletal filaments and molecular motors (FIG. 5), classifying them by the symmetry of their structures and active stresses.

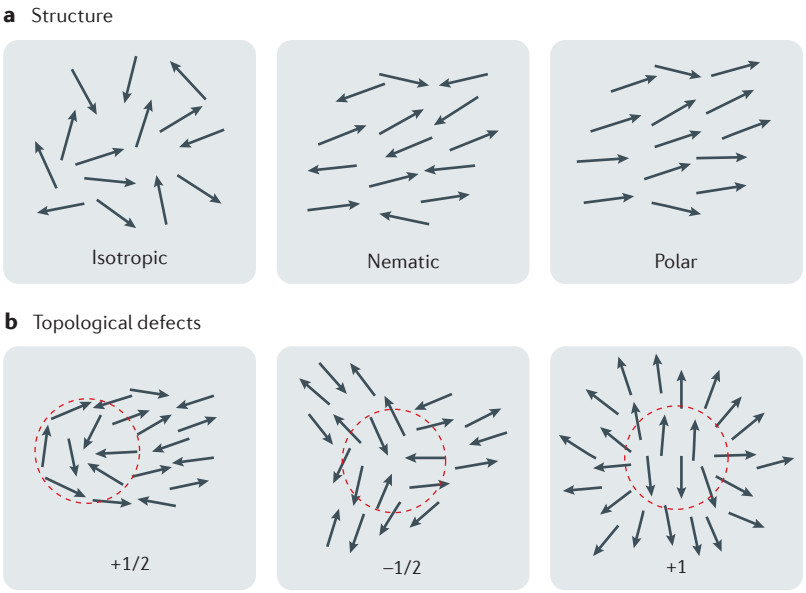

Figure 3 | **Symmetries of filament assemblies and topological defects. a** | Filaments, which are polar objects, can collectively form arrangements with different symmetries. Unoriented filaments form isotropic assemblies. A nematic arrangement can be obtained if filaments point either way along a common axis. If filaments point in a common direction, a net polar order develops. **b** | Different topological defects can be present in ordered materials, such as nematic or polar liquid crystals. The magnitude and sign of the defect's charge, which depend on the rotation of the orientation of the filaments along a path encircling the defect (red circles), give the extent and direction of the rotation of the alignment around the defect. Nematic liquid crystals can host defects with half-integer or integer charge, whereas polar liquid crystals can only host defects with integer charge.

Active extensile fluids. The dynamical behaviour of aster-forming microtubules is strikingly transformed by adding non-adsorbing polymers that interact with microtubules by excluded volume interactions and induce their bundling[46,47]. The bundling transition is driven by the gain in entropy of the depleting polymers. A single kinesin motor binds and walks along one filament, and thus cannot generate stress. By contrast, kinesin clusters can simultaneously bind multiple microtubules in a bundle. Their ability to generate active stresses depends on the polarity of the constituent microtubules. For unipolar bundles, motors simply move along two filaments towards their plus ends, without generating any interfilament sliding. In comparison, for mixed-polarity bundles, motors power interfilament sliding, which in turn generates active stresses that are predominantly extensile (in the dipolar sense; FIG. 4). Compared with the aster-forming dilute isotropic suspensions discussed above, kinesin clusters power interfilament sliding more efficiently within dense bundled microtubules, making extensile bundles a versatile building block for the assembly of diverse bulk active materials. It is likely that the effective processivity

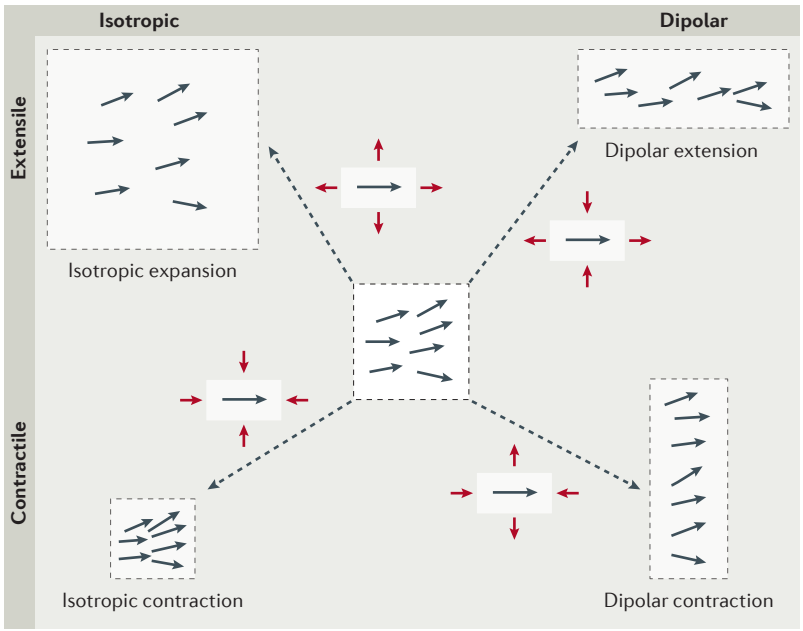

Figure 4 | **Active stresses in active materials.** Active stresses can have different symmetries and signs. In this schematic depiction, stresses are represented by red arrows. If individual elements tend to pull together in all directions, an isotropic contractile deformation will result, whereas pushing them apart in all directions produces an isotropic expansion. If the stresses produce an expansion along the long axis of the individual elements and a contraction in the orthogonal direction, a dipolar extensile deformation is obtained; the opposite case (contraction along the long axis of elements and expansion in the orthogonal direction) produces a dipolar contractile deformation. In this schematic figure, individual filaments are indicated as being the elemental units of active stress generation. In reality, the appropriate elemental unit might be a pair of filaments, a bundle or an aster.

of motor clusters moving along aligned bundles is significantly higher than that of equivalent clusters moving along microtubules in isotropic networks, but the effective processivity in aligned bundles has not been measured yet.

At high microtubule concentrations (1 mg ml^{-1} or more), extensile microtubule bundles form a percolating 3D network whose non-equilibrium dynamics is fuelled by efficient kinesin motors and can thus persist for tens of hours[48,49]. In the steady state, the dynamics of this extensile network is composed of repeating cycles in which active bundles self-extend, buckle, fracture and re-anneal with the background network (FIG. 5a). Because they are systematically built from the bottom up, the active microtubule gels and the associated turbulent-like flows display highly tunable dynamics. For example, the speed of kinesin motors that drive active gel dynamics is controlled by ATP concentration[50], which also determines the rate of active stress generation. With increasing ATP concentration, the mean square displacement of passive beads, which are advected by the turbulent-like flows of the background fluid, transitions from sub-diffusive, to super-diffusive, to ballistic[49]. Although these behaviours constitute typical features of isotropic active networks, there is limited theoretical understanding of macroscopic properties of active gels, and how they depend on the dynamics of microscopic constituents. Because the pore size of active microtubule networks is several micrometres, it is likely that any quantitative description will need to account for both the network itself and its coupling to the surrounding fluid.

Active contractile gels. Whereas the extensile stresses in microtubule-based active gels described above drive complex steady-state flows, assemblies of actin filaments and associated myosin motors exhibit very different behaviours. Studies of actomyosin active gels date back many decades, as both actin and myosin, the main components of the skeletal muscle, were identified in the first half of the 20th century[51]. Using these purified components, in 1942 Albert Szent-Györgyi demonstrated that on addition of ATP, actomyosin gels undergo a macroscopic isotropic contraction[52]. He proposed that the force generation of skeletal muscle results from such actomyosin contractions. It was subsequently discovered that contractile stresses generated by actomyosin play an important part in a much wider range of cell biological processes, including tissue migration, division and morphogenesis[53].

Myosin-II is a non-processive motor. However, at low ionic strength, myosin-II assembles into multimotor clusters, which can simultaneously bind multiple actin filaments and thus generate active stresses. Besides actin and myosin, the macroscopic contraction of actomyosin gels (FIG. 5b) requires a finite concentration of passive actin crosslinkers[54–56]. Depending on the crosslinker concentration, the contraction can result in the formation of either local clusters or a globally collapsed state[55,57]. Active contractions have also been observed in microtubule gels[58]; upon polymerizing microtubules in *Xenopus* egg extracts, the resulting network undergoes a dynein-dependent isotropic contraction that appears remarkably similar to the behaviour of actomyosin gels.

Upon collapse, the active dynamics of reconstituted contractile networks ceases, which makes it difficult to assemble non-equilibrium materials that attain long-lived steady states. This is not the case *in vivo,* where cytoskeletal filaments frequently undergo rapid turnover. For instance, the actin cortex in cells exhibits continuous pulsatile contractions driven by myosin motors, which play an essential part in diverse developmental processes[59–62]. Reconstructing such steady-state dynamics would provide another route for the assembly of synthetic active matter, and thus remains a desirable but elusive goal. Intriguingly, experiments performed on a reconstituted actin cortex in emulsion droplets exhibited large-scale flows that were somewhat reminiscent of biological processes[63].

Several models have been proposed to explain the microscopic origin of contractile active stresses in both actin-based and microtubule-based systems; these models typically consider isotropic contractile stresses. One possibility is that the macroscopic contraction arises from the intrinsic tendency of molecular motors to accumulate at filament ends[58,64,65]. In this model, the end-localized motors cause the clustering of filament ends and the formation of asters. In a subsequent step, motors simultaneously bind polarity-sorted segments of neighbouring asters, driving their collapse onto each other, thus leading

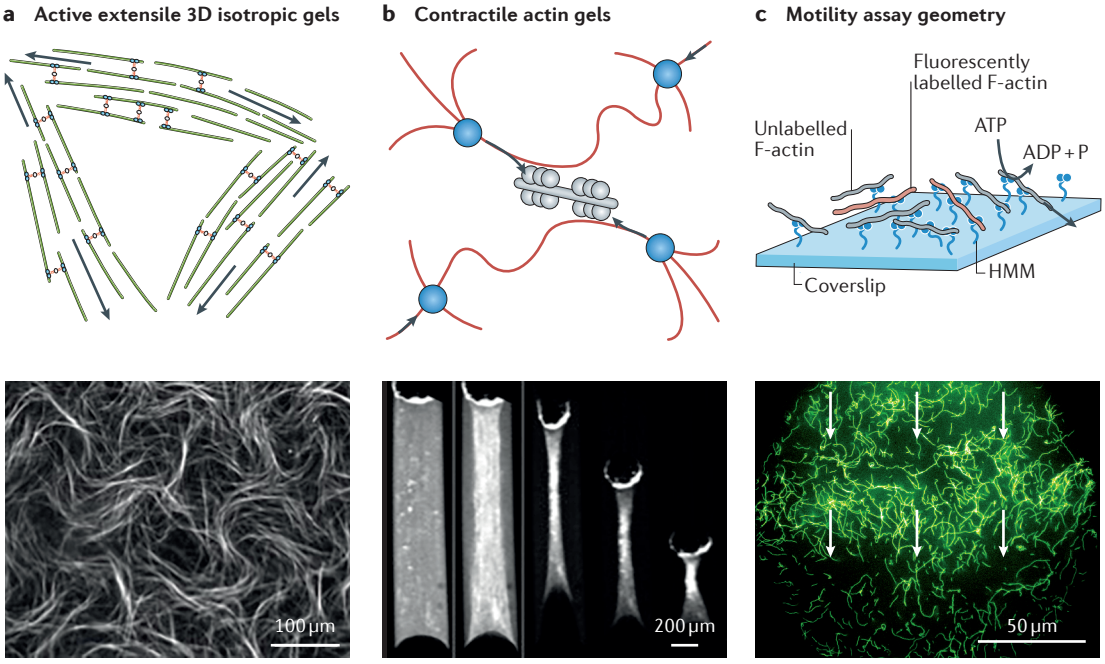

Figure 5 | **Synthetic active matter systems assembled from cytoskeletal components. a** | Clusters of kinesin motors power the extension of microtubule bundles. At intermediate densities, extensile microtubule bundles form an active isotropic fluid. The turbulent-like and autonomous fluid flows are powered by repeating cascades of extension, buckling, fracturing and self-healing of the constituent extensile bundles. **b** | Myosin motors organize into bipolar mini-filaments, which simultaneously bind to and move along multiple actin filaments, as shown in the schematic depiction (top). Myosin-motor-generated active stresses power macroscopic contractions of an entangled network of actin filaments. The sequence of images shows the contraction of a macroscopic network sandwiched between two oil droplets in glass capillaries with an inner diameter of 400 µm. **c** | In a conventional motility assay, a dense carpet of molecular motors immobilized on a solid surface propels the continuous motion of filaments, which can persist for hours. At high crosslinker densities, gliding actin filaments self-organize into a dynamical polar liquid crystal, in which dense bands composed of aligned actin filaments (indicated by the arrows) coherently move in one direction, forming density waves[169]. ADP, adenosine diphosphate; ATP, adenosine triphosphate; HMM, heavy meromyosin. Panel **a** is adapted with permission from REF. 49, Macmillan Publishers Limited. Panel **b** is adapted with permission from REF. 54, Cell Press. Panel **c** is adapted with permission from REF. 169, National Academy of Sciences.

to macroscopic contraction. This model quantitatively explains the structure, dynamics and response to perturbations of the contractile microtubule networks in *Xenopus laevis* egg extracts[58]. Alternative models based on the nonlinearity of the network mechanics or on the buckling of individual filaments have been proposed to explain contractile active stresses in actomyosin systems[66,67]. The buckling model is rooted in the observation that thin actin filaments can sustain large tensile stresses but readily undergo an Euler buckling instability in response to compressional stress. The addition of any passive crosslinker will provide a stagnation point, leading to the generation of a contractile stress that breaks the contraction/extension symmetry. Buckling has been observed both in synthetic stress bundles and in quasi-2D active actin gels[68,69]. The relative importance of different models remains unclear, and there may be other mechanisms that could give rise to isotropic contractile stresses in systems of filaments and molecular motors. To determine the relevance of the different proposed mechanisms, it will be essential to quantitatively measure both the active stresses and the mechanical properties of these systems, and relate them to the microscopic dynamics of their components.

Active nematics. The elemental motif of extensile microtubule bundles can be used to assemble diverse soft active materials. For example, sedimenting bundles onto a surfactant-stabilized oil/water interface leads to the formation of dense quasi-2D active nematic liquid crystals (FIG. 6a,b). Early theoretical modelling predicted that, in contrast to their equilibrium analogues, uniformly aligned active nematics are inherently unstable[9]. This is indeed observed in experiments on microtubule-based active nematics[49]: active stresses amplify any bend fluctuation, which subsequently grows in amplitude. Above a critical deformation, the nematic director field self-fractures, generating a 1D fracture line that is terminated by a pair of oppositely charged disclination defects of charge 1/2 (REF. 70). The structural anisotropy of +1/2 defects endows them with finite speed, whereas symmetric −1/2 defects are largely non-motile. In the steady state, microtubule-based extensile active nematics exhibit chaotic dynamics, in which topological defects are continuously generated through bend instabilities and stream through the sample until they are annihilated by defects of opposite charge[71–74].

For thick nematic films, anisotropic +1/2 defects have random orientation. Surprisingly, with decreasing

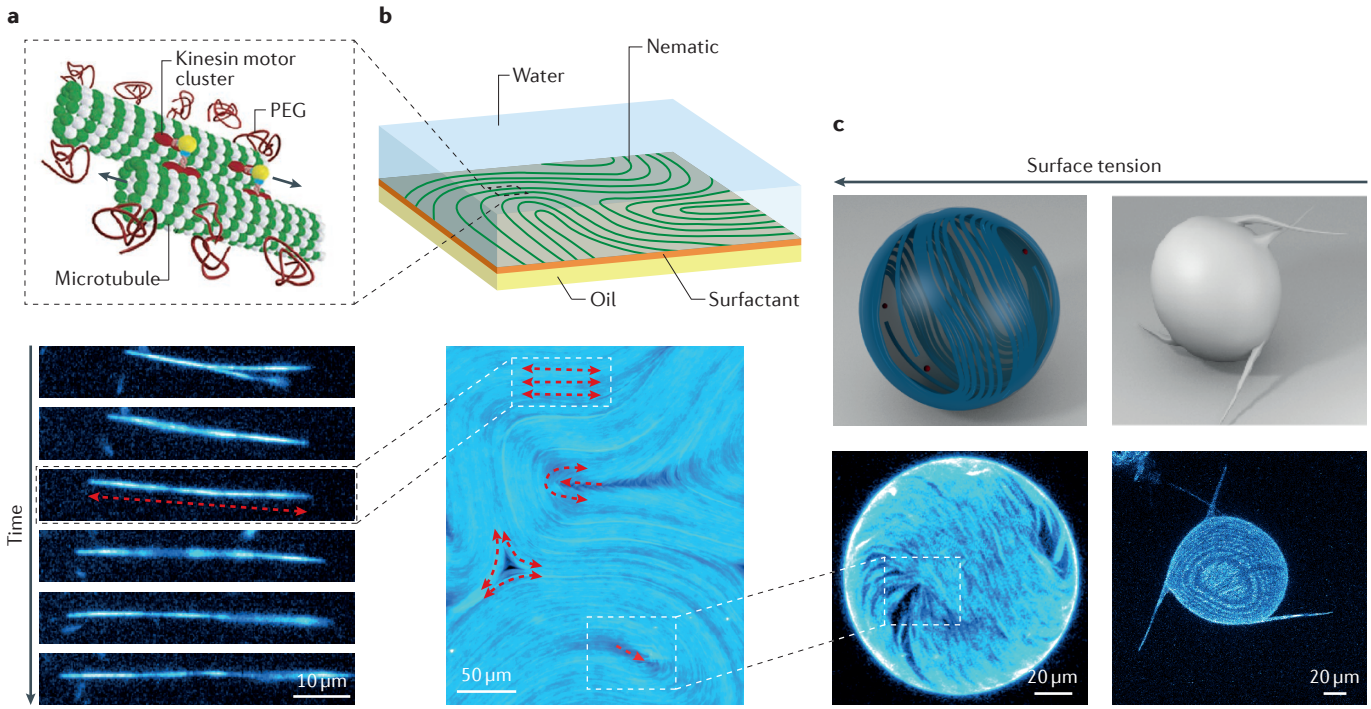

Figure 6 | **Machines built from machines: surface-confined active nematics drive cell-like protrusions and deformations. a** | The schematic and experimental images show an isolated microtubule bundle, the extension of which is driven by clusters of kinesin motors. Motors bind two neighbouring filaments, and, as they move towards the microtubule plus ends, they power microtubule sliding and bundle extension. The images are taken 5 seconds apart. PEG, polyethylene glycol. **b** | A schematic and experimental image of a dense quasi-2D active nematic liquid crystal composed of extensile microtubule bundles such as those shown in panel **a**. The dense microtubule layer is deposited at a surfactant-stabilized oil/water interface. Topological defects with charge +1/2 and −1/2 form, as highlighted on the fluorescence microscope image at the bottom. The active extensile stresses effectively cancel around more symmetric −1/2 defects. They exert a net propulsive force on anisotropic +1/2 defects endowing them with motility. **c** | Covering the inner surface of a vesicle of an emulsion with an active nematic leads to the assembly of motile topological defects of charge +1/2 that continuously oscillate between tetrahedral and planar configurations. Powered by streaming defects, confined emulsion droplets exhibit active random motion. On decreasing the tension of the lipid vesicle, four motile defects drive the assembly of filopodia-like structures that move along the surface, yielding an artificial machine that exhibits life-like properties, yet is composed of only four components. The vesicle is shown in the top panel, and confocal images showing its *z*-projection in the bottom panel. Panels **a** (top) and **b** are adapted with permission from REF. 75, Macmillan Publishers Limited. Panel **a** (bottom) is adapted with permission from REF. 49, Macmillan Publishers Limited. Panel **c** is adapted with permission from REF. 100, AAAS.

thickness, these anisotropic defects spontaneously acquire an orientational order and form a supramolecular defect-based active nematic that spans macroscopic samples and persists over many hours, even though the lifetime of the constituent defects is orders of magnitude shorter[75]. Theoretical models also predict defect-based ordered states, although with polar symmetry rather than the experimentally observed nematic symmetry, or with even more exotic defect-based ordered structures with a square lattice[76–78].

Besides microtubule-based nematics, active nematics have been studied in shaken granular rods, in motile and dividing cells[79,80], and in a composite material comprising lyotropic liquid crystals and motile bacteria[81]. Because of their preference for oxygen-rich environments, motile bacteria in this system spontaneously establish a density gradient, allowing the exploration of the entire phase diagram in a single experiment. This work demonstrated that the transition to the turbulent-like state is preceded by a regime in which bacteria form bands with continuous bend distortions.

Coarse-grained theoretical models qualitatively describe the dynamics of active nematics characterized by defect unbinding, motility and annihilation. The comparison of the defect motion with the predictions from such models demonstrates that stresses in microtubule-based active nematics are extensile (in the dipolar sense; FIG. 4). However, quantitative comparisons between theory and experiments have not yet been made. In equilibrium systems, temperature has a fundamental role in theoretical models and can be easily controlled experimentally. Active stresses have a similarly important role in active matter systems but are more difficult to tune independently of other properties of the system. For example, kinesin motors not only generate active stress but also act as passive crosslinkers[82], particularly at low ATP concentrations. Therefore, ATP concentration changes not only the magnitude of the active stress

generation but also the elasticity of the liquid crystal. It is thus challenging to map the ATP concentration directly onto theoretical parameters that quantify the magnitude of the active stresses. This issue constitutes a considerable obstacle in the quest for quantitative models of active nematics. More fundamentally, the microscopic origin of the extensile stresses that drive non-equilibrium flows in these systems remains unknown. Microscopic simulations have been performed for nematic liquid crystals powered by multi-motor clusters, and active extensile stress has been ascribed to polarity sorting of anti-aligned microtubules, as well as to crosslink relaxation of polar aligned microtubules[73,83,84]. However, experimental tests of these ideas are still lacking.

Quasi-2D active nematics have been assembled at the interface between an isotropic liquid and a thermotropic smectic liquid crystal[85] (that is, a smectic liquid crystal composed of molecular rods whose ordering is determined by temperature). The viscosity of the smectic substrate is pronouncedly different in the directions parallel and perpendicular to the smectic layers, and this alters the dynamics of the active nematics, inducing their alignment in the direction perpendicular to the smectic layers. The system uniformly extends along this direction, but its dynamics is interrupted by a bend instability that is correlated over the entire sample and that occurs with remarkable temporal regularity. This work demonstrates robust coupling of active liquid crystals to conventional liquid crystals, opening up a powerful new method to drive thermotropic liquid crystals away from equilibrium.

Active polar liquid crystals. Although microtubules are polar objects, in the active liquid crystals discussed so far they assemble into materials with nematic symmetry. Thus, they are orientationally ordered, but have no net polarity. Active liquid crystals with polar order have also been assembled, by exploiting the geometry used in previously developed biochemical motility assays. In a conventional motility assay, a coverslide surface is coated with a dense layer of molecular motors. Filaments that land on this surface will bind to it, and are propelled forward by the affixed molecular motors, generating a continuous gliding motion[86,87]. Initially, motility assays were used in the low-density single-filament limit to elucidate how various classes of molecular motors transform chemical energy into mechanical motion. More recent experiments have explored the dynamical states that emerge at higher crosslinker densities in which gliding active filaments interact with each other[88] (FIG. 5c). With increasing actin concentration, the gliding filaments undergo a transition from an orientationally disordered state to an orientationally ordered state with polar symmetry, formed by high-density travelling bands of coherently moving filaments with the same orientation. In contrast to nematic phases, which can exhibit defects of charge 1/2, the symmetry of polar phases only permits defects with integer charges. In the polar active phase that we are discussing, only +1 defects were found, which clearly illustrates the fundamental difference between this kind of system and active nematics. The simplicity of the motility assay geometry allowed the quantification of the low-density binary collision statistics of the gliding filaments, which was studied in an attempt to understand how the microscopic dynamics of the constituent units leads to macroscale patterns. The high-density patterns cannot be explained by kinetic models based on binary collisions, suggesting that many-body effects need to be taken into account when connecting microscopic dynamics to collective behaviours[89]. More recently, collective phenomena have also been explored in gliding microtubules that are powered by dynein motors[90]. In this system, the gliding filaments form vortex-like patterns; this difference in macroscopic patterns could be due to different collision dynamics of gliding actin filaments and microtubules. Besides cytoskeletal components, polar order has been studied in shaken granular materials and in externally driven Quincke rollers[91–93]. However, all strategies used for assembling polar active liquid crystals require their attachment to a substrate. Extending these methods to obtain bulk active polar liquid crystals remains a challenge.

Confined active matter. So far, we have described the dynamics of bulk active fluids and gels of varying symmetries and the mechanisms of stress generation. In contrast to these unbounded systems, most non-equilibrium processes in cell biology take place in confined environments. Motivated by this observation, efforts were undertaken to understand the influence of confinement and boundaries on active matter, and how they lead to the emergence of new patterns and dynamical states. For example, work across many length scales, ranging from entire organisms to motile bacteria to cellular tissues, has demonstrated that confinement effectively and generically transforms chaotic dynamics of diverse 2D active systems into persistent circular currents[94–97]. Recent experiments have extended such studies to bulk microtubule-based extensile fluids, demonstrating that 3D confinement transforms chaotic bulk dynamics of bulk fluids into long-ranged coherent flows that persist on macroscopic scales[98]. In comparison to previous studies, the transition in the microtubule-based fluids seems to be an inherently 3D phenomenon and is not observed in systems with reduced dimensionality. Quantitative experiments have shown that the location of the transition from chaotic to coherent flows is determined by a universal scale-invariant criterion that is related to the profile of the confining geometry[98]. Simultaneously, structural imaging has demonstrated that the formation of coherent flows is accompanied by the formation of a nematic layer that wets the boundaries at a well-defined oblique angle, and that the active stresses generated by this layer power the coherent fluid flow[98].

The chaotic dynamics is a generic feature of intrinsically unstable active nematics. By contrast, although the mitotic spindle is well described as an active nematic system, it retains a uniform alignment throughout its entire structure because of its finite size[99]. This observation clearly demonstrates that boundary effects also strongly influence the behaviours of active nematics. In this spirit, active nematics have been confined on the inner surface

of a spherical vesicle or an emulsion droplet[100] (FIG. 6c). The spherical topology ensures that the total charge of the surface-bound topological defects is +2 (REF. 101). The simplest case comprises four +1/2 motile defects streaming on the spherical surface. In this limit, the motile defects oscillate between planar and tetrahedral configurations with a well-defined frequency. Changing ATP concentration varies the oscillation frequency, thus demonstrating that spherically confined active nematics can form tunable, persistent oscillators. Furthermore, decreasing the vesicle's surface tension couples the motile defects to the vesicle's deformation modes, leading to the generation of four filopodia-like protrusions, with the entire dynamical assemblage assuming the appearance of a life-like cell, despite consisting only of four distinct components (FIG. 6c). Streaming flows of cortical nematics can also power Brownian-like motility of the entire spherical vesicle[49]. The challenge now is to control the defect dynamics in order to determine the droplet motion. A rolling active droplet is an example of a mesoscopic machine that is assembled from and powered by nanosized machines. It also illustrates how bottom-up studies of active matter allow the assembly and exploration of dynamical assemblages that, even though they have no direct biological relevance, are interesting from the perspective of materials science.

Active matter in cell biology

The rich behaviours of active matter assembled *in vitro* discussed above are driven by motor-generated active stresses[9,102]. Active stresses are also believed to have an important role in many cell biological processes. If these active stresses are small enough not to generate coherent flows, they can be experimentally studied using microrheology to measure their fluctuations. Microrheology can be performed actively, by directly measuring the mechanical properties of the medium under study through the application of known forces, or passively, by observing the spontaneous fluctuations of particles imbedded in the medium[103]. In an equilibrium sample, the motion of particles is caused by thermally driven stress fluctuations, which are related to the mechanical properties of the sample by the fluctuation–dissipation theorem. The additional active stresses in non-equilibrium materials lead to enhanced motions and to the breakdown of the fluctuation–dissipation theorem. Studying the differences between active and passive microrheology measurements provides a means to quantify the violation of the fluctuation–dissipation theorem and thus measure the non-equilibrium fluctuations generated by active stresses[104–106]. Such active stress fluctuations have been observed and quantitatively studied in a variety of cell biological systems, including entire cells[107,108], the cytoplasm[104,109,110], subcellular membrane-bound structures[111,112] and spindles[99]. In many (but not all) of these systems, active stress fluctuations vary with the frequency ω as $1/\omega^2$, a dependence that has also been observed in *in vitro* networks of purified actin and myosin[105]. A $1/\omega^2$ spectrum of stress fluctuations can arise in active liquid crystal theories owing to orientational fluctuations[99] or through a step-like binding and unbinding of molecular motors to the cytoskeleton[113]. Active stress fluctuations not only provide a tool to study the non-equilibrium mechanics of cell biological systems, they may also have a functional role. It has been proposed that active stress fluctuations may help to mix and transport objects through the cytoplasm[110], and that related processes position the nucleus in mouse oocytes[114]. Active stresses can also strongly modify the rheology of materials. Such phenomena have not yet been quantified in a cell biological context, but it has been demonstrated that activity in dense bacterial suspensions reduces the effective suspension viscosity to zero[115]. Microrheological measurements of stress fluctuations are only possible in systems that are in a steady state and in which active stresses do not cause coherent large-scale flows. Although such conditions are commonly observed in cells, they are challenging to realize *in vitro*, so most studies of active stress fluctuations have been performed on complex living systems. For regimes in which microrheology fails, no techniques are available to quantify active stresses.

In addition to the localized fluctuations described above, sufficiently large active stresses can produce large-scale deformations and flows, which are important for many cytoskeletal-based processes. The theoretical formalism of active matter provides a promising framework for understanding such phenomena. Active matter theories have recently been used to interpret experiments on a wide variety of actin-driven processes, including flows in the actin cortex[60,116], bleb formation due to detachment of the actin cortex from the membrane[117], cytokinesis and shape changes occurring during cell division[118–120] (FIG. 7a) and cell motility[121–123]. In many cases, the observed motions and flows are well captured by theory. Even highly simplified models can exhibit behaviours that look remarkably similar to those of actual biological systems[124,125]. One challenge in performing detailed tests of these theories is that they postulate that motions result from the combined effect of coarse-grained active stresses and passive material properties, which are very difficult to measure independently. In the absence of direct force/stress measurements, it is only possible to extract ratios of mechanical properties. For example, the ratio of viscosity, η, to friction, γ, sets the characteristic length scale of stress propagation, $\lambda = \sqrt{(\eta/\gamma)}$, which is ~70 μm for the actin cortex in a zebrafish embryo, as estimated using the response to laser ablation[126] (FIG. 7b), and ~350 μm for microtubule networks in cell extracts, as determined by studying the sample in controlled geometries[58].

Active matter theories have been used to study the self-organization of a wide variety of subcellular structures. This requires an understanding not only of the behaviours of stresses and flows, but also of a range of other factors, such as the density and orientation of the filaments from which these structures are composed. The resulting theories necessarily contain many terms, whose relevance and form can be difficult to test directly, and many parameters, whose values can be challenging to measure. One powerful approach for the investigation of these issues in non-equilibrium steady-state systems is through spatio-temporal correlation functions of fluctuations, which are intimately related to

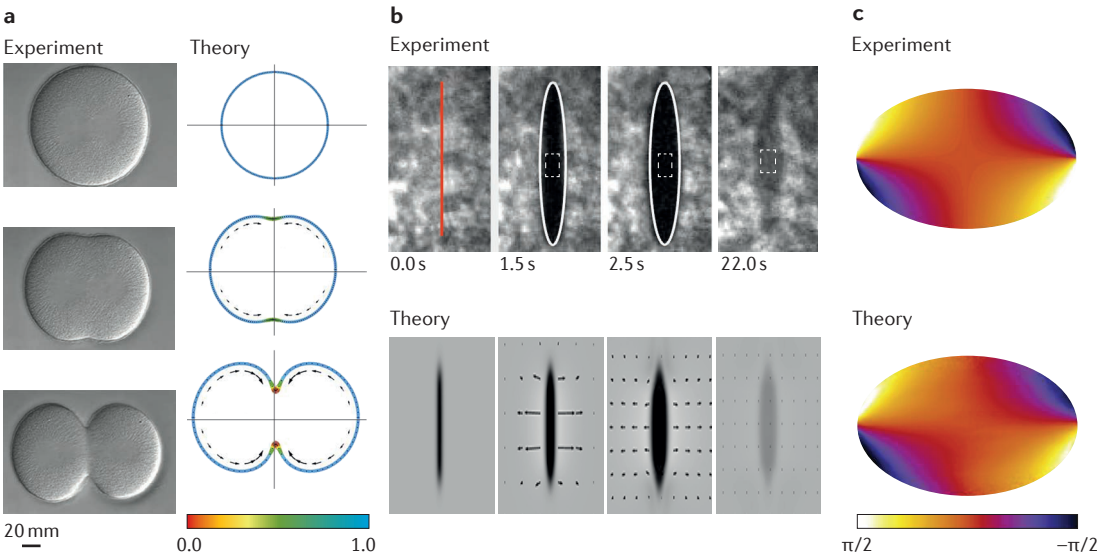

Figure 7 | **Theory and experiments on subcellular structures.** Active matter theories can capture the behaviours of self-organized subcellular structures. **a** | The morphological changes of a dividing sea urchin embryo are well captured by an active matter theory that accounts for the actomyosin-driven contractions of the cell cortex furrow constriction in animal cell cytokinesis[119]. **b** | The response of the actin cortex to laser ablation is well described by an active matter theory of the mechanics and turnover of the cell cortex[126]. The panels show laser ablation at time 0 s (left) followed by mechanical deformation and recovery by turnover. **c** | An active liquid crystal theory quantitatively describes the shape of the spindle and the orientation of microtubules inside it[99]. Panel **a** is adapted with permission from REF. 119, Cell Press. Panel **b** is adapted with permission from REF. 126, Cell Press. Panel **c** is adapted with permission from REF. 99, National Academy of Sciences.

the equations of motion and can be measured under a microscope and theoretically calculated. Studies of this type have revealed that an active liquid crystal theory can quantitatively describe the statistics of spontaneous fluctuations of microtubule density, orientations and stresses in spindles, both validating the use of this theory for describing the spindle and allowing nearly all of the parameters to be measured[99]. The same theory can quantitatively explain the morphology of the spindle (FIG. 7c), even though capturing its size requires incorporating additional processes that spatially regulate microtubule nucleation[127]. Similar active matter theories have been used to understand the self-organization of the actin cortex and its interplay with the organization of lipid-tethered proteins in the plasmid membrane[128].

Inside cells, cytoskeletal filaments are not only transported by molecular motors, but they also continuously and rapidly polymerize and depolymerize. For example, actin cables in budding yeast (micrometre-long filamentous bundles) maintain the same structural appearance over many minutes; however, if actin assembly is inhibited, the entire cable disappears within tens of seconds[129]. Numerous other cytoskeletal structures, including mitotic spindles, cilia, the actin cortex and filopodia, appear static but are actually in a highly dynamical steady state, wherein the constituent monomers rapidly and continuously exchange while maintaining large-scale structural integrity. Microscopic turnover dynamics endows these cytoskeletal structures with their unique properties, such as adaptability, rapid shape changes and self-healing ability. The examination of monomer turnover in reconstituted system has been limited. A study inspired by the pathogen *Listeria monocytogenes* demonstrated that actin polymerization forces can endow micrometre-sized beads with motility[130]. Similarly, microtubule polymerization forces have been measured by quantifying how a growing filament pushes on a obstacle[131]. It is very likely that the interplay between turnover and motor-generated contractile stresses is important for maintaining many cell biological structures in a non-equilibrium steady-state[131]. Their combination also provides a promising, albeit currently unexplored, route for the construction of new forms of synthetic active matter.

The molecular motors and filament polymerization dynamics that underlie biological self-organization are regulated by a myriad of signal pathways. Understanding the interplay between biochemical regulation and active matter is a key challenge for the future[132]. Theoretical models have recently explored the formation of patterns generated by active stresses that advect chemical species, which in turn can control the magnitude of active stresses through chemical reactions[133]. It has been suggested that this mechanism might be responsible for the temporal formation of pulsatile patterns that are observed in the actin cortex of biological cells[134].

Active matter beyond the cytoskeleton. We have focused on the cytoskeleton, but it is likely that the collective behaviours of molecular machines have an important role in a much wider array of cellular structures. For example, the large-scale motions of eukaryotic chromosomes in the nucleus have been proposed to be

driven by DNA-binding enzymes that act as motors[135,136], and active motion has been observed in nuclei of prokaryotes[137]. Furthermore, many properties of chromosomes, including detailed features of the organization of interphase and mitotic chromosomes and the process of chromosome condensation, can be explained by models in which molecular motors slide DNA strands relative to each other, producing loops[138–141]. This suggests that molecular motors may be as fundamental to chromosome organization as they are to cytoskeleton organization. Synthetic active gels of DNA and DNA-binding molecular motors have also been studied, but this area requires further exploration[142,143].

Another cell biological domain in which non-equilibrium collective behaviours have important roles is membranous systems, which are central to many aspects of cell biology, from protein synthesis to signalling and to secretion. However, despite several exciting studies, the cellular biophysics of these processes remains under-researched[128,144–146]. From a synthetic perspective, some of the first active matter studies quantified non-equilibrium fluctuations driven by protein pumps, which generate unidirectional currents of protons through the membrane[147–150].

Active matter at different scales. Equilibrium self-assembly requires significant thermal fluctuations to allow the system to explore different configurations; thus, it is only viable if the constituents of the system are sufficiently small. By contrast, active matter has no such limitations and exhibits self-organization at multiple length scales, leading to hierarchical assemblages. The subcellular biological systems discussed above determine the behaviours of cells, which in turn compose tissues; tissues form organisms; organisms can self-organize into flocks and herds. Each of these levels is being studied from the perspective of active matter. For instance, active contractions are believed to drive the internal organization and shape of tissues and are thus central to morphogenesis[151–154]. At larger length scales, the collective behaviours of groups of organisms, such as swarms of locusts and flocks of penguins, have been studied[94,155]. In addition to work on animals, emergent behaviours of microorganisms have also been extensively investigated[156–158]. Experiments in this area have illustrated collective turbulent-like dynamics emerging in dense bacterial suspensions, as well as complex patterns emerging in confined active fluids[81,95,159,160].

Active matter in chemical systems. An ambitious goal is the assembly of active materials that are entirely built from chemically synthesized components. Because they are more robust against environmental perturbations compared with those assembled from purified cytoskeletal components, such materials are probably the only feasible way to construct active materials for use in practical applications. An example involves the synthesis of phoretic Janus swimmers, which locally catalyse molecular fuel, create gradients in the chemical products and acquire motility because of such gradients. Extensive experiments have explored the individual dynamics and collective behaviours of such motile swimmers, revealing that isotropic swimmers, which exert no torque on each other, tend to cluster and phase-separate, whereas rollers, which exert torques on each other, tend to form collective flocks[92,161–164]. A challenge in this area is the lack of high-efficiency artificial micromachines that exhibit different motility patterns. For example, the efficiency of phoretic swimmers is many orders of magnitude smaller than that of biological motors, which has so far limited the study of chemically synthesized systems to two dimensions[165].

In experiments with purified materials, either isolated from nature or synthesized in the laboratory, the dynamical state that forms is set by extrinsic parameters, such as particle concentration. By contrast, cells use intrinsic regulatory feedback mechanisms, which continuously sense their environment and consequently select a dynamical state. Implementing such regulatory schemes in any artificial system remains a substantial and unrealized challenge. To accomplish this, it is essential to imbue active systems with sensing mechanisms and the ability to reconfigure and switch between multiple dynamical states. Constructing new artificial active materials is likely to require input from diverse scientific communities, including engineers, materials scientists and chemists.

Conclusions

Given the architecture and interactions of specific molecular building blocks, the formalism of equilibrium statistical mechanics predicts with remarkable precision the range of all possible large-scale structures that they can form. For example, equilibrium statistical mechanics explains why amphiphilic lipids assemble into vesicles and block-copolymers form lamellae and other microphase-separated structures. In comparison to our advanced knowledge of equilibrium self-assembly, the current understanding of how large-scale structures and patterns emerge in cellular environments and synthetic, internally driven, out-of-equilibrium materials is still in its infancy. A theoretical formalism that predicts the space of all possible emergent states of machines made from machines has not yet been formulated but would have profound impact on both biology and materials science. Understanding self-organized biological structures within this broader framework will not only reveal the mechanisms that drive their formation and behaviour but might also provide insight into possibilities available for their evolution. Just as the laws of fluid mechanics place constraints on the structure and dynamics of swimming organisms, the principles of active matter may constrain the form and function of many subcellular structures. Furthermore, a theoretical formalism of active matter capable of predicting macroscopic behaviours from the properties of the microscopic constituents would allow the systematic construction of active materials with life-like functionalities. More ambitiously, understanding the landscape of all possible states available to active systems would enable the engineering of active materials not constrained by the limitations of life, which could thus go beyond biology.

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