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REVIEW ARTICLE

The Actomyosin Cortex of Cells: A Thin Film of Active Matter

*K. Vijay Kumar**

Abstract | The actomyosin cortex is a thin film, containing actin filaments and myosin molecular motors, located beneath the plasma-membrane of eukaryotic cells. Active processes, driven by ATP hydrolysis, can generate mechanical forces in the cortex. Coordinated force-generation drives large-scale mechanical flows and orientation patterns. These flows can pattern proteins coupled to the cortex leading to the emergence of active mechanochemical patterns. In this review, we discuss physical approaches to understand force-generation and the concomitant patterns observed in the actomyosin cortex. We briefly outline the hydrodynamic theory of active gels as applicable to the cortex and discuss its consequences. We speculate on the role of the actomyosin cortex in sculpting large-scale tissues and end with an outlook for open problems.

1 Introduction

The eukaryotic cytoskeleton is a self-organized structure consisting of polymeric filaments, molecular motors, cross-linkers and other assorted proteins that together provides a mechanical framework for the cell. A remarkable property of the cytoskeleton is the ability of molecular motors to transduce energy released in chemical reactions, such as the hydrolysis of adenosine triphosphate (ATP), into mechanical force. This is the primary mechanism of force generation in cells and tissues in a very wide range of living systems[1–3]. The mechanical forces thus generated are implicated in various cellular processes such as cargo transport, chromosome segregation, cytokinesis, cellular shape, cell motility, and are also involved in moulding tissues at a larger scale[4–8]. Tremendous progress in the past few decades has opened novel vistas into the cytoskeleton as a master regulator of mechanochemical processes at various spatial and temporal scales. In particular, highly interdisciplinary research approaches are beginning to uncover the fundamental physical principles that underlie the emergence of complex patterns in the cytoskeleton and in the various signaling proteins that the cytoskeleton regulates.

Typically, the polymeric filaments of the cytoskeleton are classified into three major components: microtubules, actin filaments and intermediate filaments. However, this classification does not imply any functional independence as the different components strongly interact with each other[9]. Microtubules, with their large persistence lengths, are primarily used to construct the various rigid structures of the cell, such as tracks for intracellular cargo transport and the mitotic spindle. The more malleable nature of the actin cytoskeleton makes it more amenable to be used for those cellular processes that require substantial deformations, such as the formation of the cytokinetic ring and cell motility. On the other hand, intermediate filaments act as stress absorbers in the cell[10]. We have significant understanding of the physics of microtubule and actin cytoskeletons, while much needs to be learnt about the physical properties of intermediate filaments[11].

It is interesting to note that there are homologs of the eukaryotic cytoskeletal filaments in prokaryotes as well, although there are no known molecular motors[12,13]. Compared to prokaryotes, the eukaryotic cytoskeleton is a rather complex mixture of many interacting components. However, this menagerie evolved much before the last eukaryotic common ancestor, and thus the cytoskeletal proteins are widely conserved. Incidentally, this also suggests that a

[1] *International Centre for Theoretical Sciences, Tata Institute of Fundamental Research, Survey 151, Shivakote Village, Hesaraghatta Hobli, Bengaluru 560089, India.*
**vijaykumar@icts.res.in*

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physical understanding of the cytoskeleton in one system can have far reaching consequences in shedding light on processes found in diverse systems.

In this review, we discuss the physics of the actomyosin cytoskeleton. In particular, we will focus on the actomyosin cortex which is a thin film of actin filaments and associated proteins found just beneath the plasma membrane of eukaryotic cells. In Sect. 2, we outline various approaches to understand force generation in the cortex. Next, in Sect. 3, we discuss coarse-grained active hydrodynamical theories of the cortex. We then turn, in Sect. 4, to discuss several cellular processes, such as cell division, polarity and motility, that are largely driven by the active processes in the actomyosin cortex. We also address in vitro reconstitution studies of the actomyosin cortex in this section. Collections of cells, either in epithelial tissues or in spreading monolayers, are discussed in Sect. 5 with an emphasis on the role of the actomyosin cortex in regulating their dynamics. This section concludes with ideas on the geometrodynamics of active materials, i.e., studies in which the mechanical stresses generated in active materials can be used to mould their shapes, with potential implications for the morphology of cells and tissues. Finally, in Sect. 6, we speculate on the broad open problems in this fertile area that will require a strong cross-talk between different disciplines. It should be noted that this is not an exhaustive review of the properties of the actomyosin cortex of animal cells. Rather, our approach is to discuss the physics underlying the cortex as a thin film of active matter containing contractile stresses, orientable filaments, and the resulting mechanical deformations and flows that generate mechanochemical patterns and shape changes in cells, and at larger scales, in entire tissues.

2 Force-Generation in the Actomyosin Cortex

The cellular cortex is a polymeric meshwork of cross-linked actin filaments lying below the plasma membrane. The primary nucleators of actin filaments are the Arp2/3 complex and formins. Interspersed in this meshwork are also molecular motors and cross-linking proteins along with those that can severe, cap and stabilize actin filaments. It is interesting to note that the cortex has long been observed as a thin layer involved in the locomotion of cells[14], but its molecular components and their control on cellular mechanics has only been recognized much later[15–17]. For some recent reviews on the actomyosin cortex, see[18–26].

Classical studies revealed a branched and cross-linked gel of actin filaments in the lamellipodial protrusions of crawling cells[27,28]. This is understood to be a consequence of actin polymerization at the leading edge of the cell coupled with Arp2/3 mediated branching. Actin filaments also form bundles and extrude the cell surface in the form of filopodial protrusions. In fact, atomic force microscopy analysis reveals that the cortex contains both bundle-like and mesh-like structures, that are regulated by the cell[29]. In non-extruding regions of the cell surface, the actomyosin cortex has a thickness of a few hundred nanometers as revealed by sub-resolution fluorescence imaging[30]. The actin cortex is, however, not a static structure. Actin filaments undergo polymerization and de-polymerization, while cross-linkers and molecular motors continuously bind/unbind to the filaments. Several of these stochastic reactions are driven by ATP hydrolysis. As such, this external energy input breaks the detailed balance between reaction rates and the associated energies of the reactants and products, that would otherwise exist in an equilibrium system. This nonequilibrium remodeling of the cortex makes it a very dynamical structure. In living cells, actin filaments disassemble on timescales of ~ 30 s[31]. It should be noted that this timescale is not necessarily the timescale on which mechanical stresses relax. The highly cross-linked and dynamical structure of the actomyosin cortex makes it behave like a viscoelastic gel (a material that resists deformations like an elastic solid at short timescales, and flows like a viscous fluid at long timescales) . Indeed, laser ablation experiments, coupled with modeling the cortex as a linear viscoelastic material, uncover a Maxwell mechanical stress relaxation time $\tau_M \sim 5$ s[32]. For processes occurring on timescales much longer than the remodeling timescale, the actomyosin cortex can effectively be treated as a complex viscous fluid. A cross-linked and dynamic meshwork of polymeric filaments responds to mechanical perturbations like a viscoelastic gel by developing internal stresses. However, the distinctive character of the actin cortex is its ability to generate active stresses in addition to the stresses present in a passive viscoelastic gel. The primary source of these active stresses is the ATP consuming activity of myosin motors that can generate mechanical forces.

Actin filaments are polar objects with a distinct fore-aft structural asymmetry. Upon binding to actin, mini-filaments of myosin motors can undergo ATP hydrolysis driven conformation changes leading to unidirectional translocation of these motors along the actin filament[1,3,33]. Sustaining this directed movement necessarily requires a polar track (the actin filament) and an energy flux (ATP hydrolysis). If the translocating myosin motor is cross-linked to a neighboring actin filament, it can tug along the nearby filament and thus exert a force. A pair of antiparallel actin filaments could thus slide past each other driven by the activity of myosin motors and ATP. Such an organized configuration of actin filaments is seen in sarcomeric structures of muscle cells[34]. In fact, our understanding of mechanochemical force transduction by molecular motors was driven to a large extent by studies of muscle contraction.

If a configuration of antiparallel actin filaments leads to contractile forces by motor activity, the opposite configuration (with reversed actin polarities) should lead to extensile forces. As such, the description of contractile forces in actin filaments discussed above only works in the case of sarcomere-like structures. However, the cortical actomyosin meshwork is not a highly organized structure like the sarcomere, and hence one would expect that the randomized configurations of antiparallel actin filaments in an unstructured gel should lead to neither contractile forces nor extensile forces. Yet, it is well known that the actomyosin cortex shows, on the average, contractile behavior. Why then are actomyosin gels contractile? Recent work in the past decade has uncovered that the nonlinear elasticity of actin filaments plays an important role in this context. Semi-flexible actin filaments buckle under contractile forces, and this breaks the apparent symmetry between contractile and extensile forces in an otherwise disorganized meshwork[35–39]. It is also possible that a polymeric meshwork consisting of semi-flexible filaments can contract even in the absence of molecular motors, provided the kinetics of polymerization–depolymerization and the binding–unbinding of cross-linkers does not obey detailed balance[40]. It important to note that the network architecture and, concomitantly, the tension in the cortex is strongly regulated by the kinetics of both actin filaments and myosin motors[31,41]. In fact, depending on the connectivity and local architecture, cortical network contraction could be dominated either by sarcomeric-like mechanisms or by buckling[42].

3 Physical Models of the Cortex

How do we construct physical models for the actomyosin cortex? In principle, one could start by microscopic descriptions using, for instance, all atom molecular dynamics simulations of all the proteins that comprise the cortex. It soon becomes evident that this is too difficult and, perhaps, not really needed inasmuch as we seek to understand the properties and functions of the cortex at the cellular level and above. A mesoscopic approach is to develop models wherein the filaments are modeled as rigid or semi-flexible rods with interspersed molecular motors and cross-linking proteins being modeled, for instance, as simple interconnecting springs. Analytical results are hard to obtain even at this level, but stochastic simulations can provide key insight on the kinetics of various processes such as the onset of contractility and network architecture[43–49]. A general conclusion that arises from mesoscopic simulation studies of the cortex is that very similar large-scale behavior can result from tuning many microscopic parameters. As such, coarse-grained approaches that can capture the essential large scale features of actomyosin networks are desirable. A successful approach developed in the past two decades is to describe the actin cortex as a thin film of an active gel and develop hydrodynamic descriptions akin to those developed in soft-condensed matter physics[50]. We next elaborate on this coarse-grained approach and briefly summarize the mathematical equations governing the spatiotemporal evolution of the hydrodynamic fields in an active gel description of the cortex. A recent survey of several non-equilibrium physics approaches to biological problems and, in particular, to the cytoskeleton can be found in Ref.[51].

Hydrodynamics is an extension of the thermodynamic description of a macroscopic system to include spatiotemporal fields that vary slowly compared to the microscopic scales. The hydrodynamic fields are typically the densities of conserved quantities (such as mass and momentum) and the densities of broken-symmetry variables (such as polar or nematic orientation fields). In a systematic derivation of the hydrodynamic equations, we first identify the generalized forces and fluxes that lead to the production of thermodynamic entropy. Appealing to Onsager's relations in the vicinity of thermodynamic equilibrium, we then expand the generalized-fluxes as a linear combination of the generalized forces[52]. These expansions represent the material constitutive relations

involving kinetic coefficients (such as the viscosities) and contain all possible terms allowed by the symmetries of the system. The requirement of time-reversal symmetry, as in the case of a system governed by equilibrium dynamics, restricts some of the possible couplings. However, for a system driven out of equilibrium, such as, for example, the cellular cytoskeleton driven by motor activity, no such requirement of time-reversal symmetry is imposed on the equations of motion, and in this case, novel active couplings are permitted[53]. For instance, couplings between chemical reaction rates and local orientational order are allowed in the expression for the mechanical stresses. These stresses are the coarse-grained representations of the active mechanochemical forces generated during ATP driven motor-filament activity.

The hydrodynamic theory of soft active materials is a very vibrant area of research. See[54–62] for recent reviews. The theories developed for three-dimensional active gels can be adapted to describe the actomyosin cortex. Specifically, we integrate the hydrodynamical equations over the thickness of the cortex to get effective two-dimensional equations. It should be noted that these equations provide a coarse-grained, but very generic, description of the cortex and are applicable on length-scales large compared to the typical size of actin filaments and on time-scales long compared to the timescales of the stochastic chemical kinetics associated with the turnover of the cortical components. We next discuss, in brief, a simplified version of the hydrodynamical equations applicable to the cortex.

We consider the cortex as a two-dimensional layer of constant thickness with uniform density of actin filaments oriented, on average, in a direction perpendicular to the plane of the cortex, as shown in Fig. 1. The in-plane orientation of these filaments is described by a polar order parameter $\mathbf{p}$ and a nematic order parameter $\mathbf{Q}$ (a symmetric traceless tensor second-rank tensor). Interspersed in this thin-film are N chemical components (myosin motors, polarity proteins, cross-linkers, other embedded proteins, etc), and the number density n_i of the ith chemical component satisfies

$$\partial_t n_i = -\nabla \cdot (n_i \mathbf{v}) + D_i \nabla^2 n_i + R_i, \tag{1}$$

wherein D_i is the coefficient of diffusion and R_i represents all the chemical reactions that can affect species i. The velocity field $\mathbf{v}$ is a solution of the hydrodynamic equation governing the conservation of linear momentum. Typical flows at the cellular and tissue levels are such that inertial effects are negligible. As such, the equation for the velocity field takes on the form of a force-balance equation:

$$\nabla \cdot \boldsymbol{\sigma} = -\mathbf{F}_{\text{ext}}, \tag{2}$$

where $\boldsymbol{\sigma}$ is the (second-rank) mechanical stress tensor, and $\mathbf{F}_{\text{ext}}$ represents all the external forces acting on the cortex and can include, for instance, the traction forces arising from the cytoplasm or the membrane. A frictional approximation $\mathbf{F}_{\text{ext}} = -\alpha\, \mathbf{v}$, with a friction coefficient α, is often employed as a simple model for these external forces.

On time-scales long compared to the viscoelastic relaxation time, the cortex can be modeled as a viscous fluid. In this limit, the constitutive equation is

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}_{\text{h}} + \boldsymbol{\sigma}_{\text{o}} + \boldsymbol{\sigma}_{\text{a}}, \tag{3}$$

where $\boldsymbol{\sigma}_{\text{h}}$ is the hydrodynamic stress arising from fluid flow, $\boldsymbol{\sigma}_{\text{o}}$ is the (passive) stress arising from the orientation fields, and $\boldsymbol{\sigma}_{\text{a}}$ represents active stresses. In the approximation of a Newtonian fluid, the hydrodynamic stress is linearly related to velocity gradients. Defining the shear-rate tensor $2\boldsymbol{\epsilon} = \nabla\mathbf{v} + [\nabla\mathbf{v}]^T$ and the vorticity tensor $2\boldsymbol{\omega} = \nabla\mathbf{v} - [\nabla\mathbf{v}]^T$, where $\text{Tr}(\ldots)$ and $[\ldots]^T$ denote the trace and transpose operations respectively, the hydrodynamic stress is

$$\boldsymbol{\sigma}_{\text{h}} = 2\eta\, \boldsymbol{\epsilon} + (\eta_b - \eta)\, \text{Tr}(\boldsymbol{\epsilon})\, \mathbb{I}, \tag{4}$$

with η and η_b being the effective shear and bulk viscosities of the cortex, and $\mathbb{I}$ the identity tensor in two-dimensions. On the other hand, for short time-scales, compared to the time-scale for the relaxation of elastic stresses, an appropriate description for the cortex is that of a viscoelastic fluid with a Maxwell relaxation time τ_{M}. In this case, the mechanical stress satisfies

$$\left(1 + \tau_{\text{M}} \frac{D}{Dt}\right)(\boldsymbol{\sigma} - \boldsymbol{\sigma}_{\text{o}} - \boldsymbol{\sigma}_{\text{a}}) = \boldsymbol{\sigma}_{\text{h}}, \tag{5}$$

where the co-moving co-rotating derivatives $\frac{D}{Dt}$ for a vector field $\mathbf{p}$ and a tensor field $\mathbf{Q}$ are defined as

$$\frac{D\mathbf{p}}{Dt} = \partial_t \mathbf{p} + \mathbf{v} \cdot \nabla \mathbf{p} + \boldsymbol{\omega} \cdot \mathbf{p}, \tag{6}$$

$$\frac{D\mathbf{Q}}{Dt} = \partial_t \mathbf{Q} + \mathbf{v} \cdot \nabla \mathbf{Q} + \boldsymbol{\omega} : \mathbf{Q} + \mathbf{Q} : \boldsymbol{\omega}. \tag{7}$$

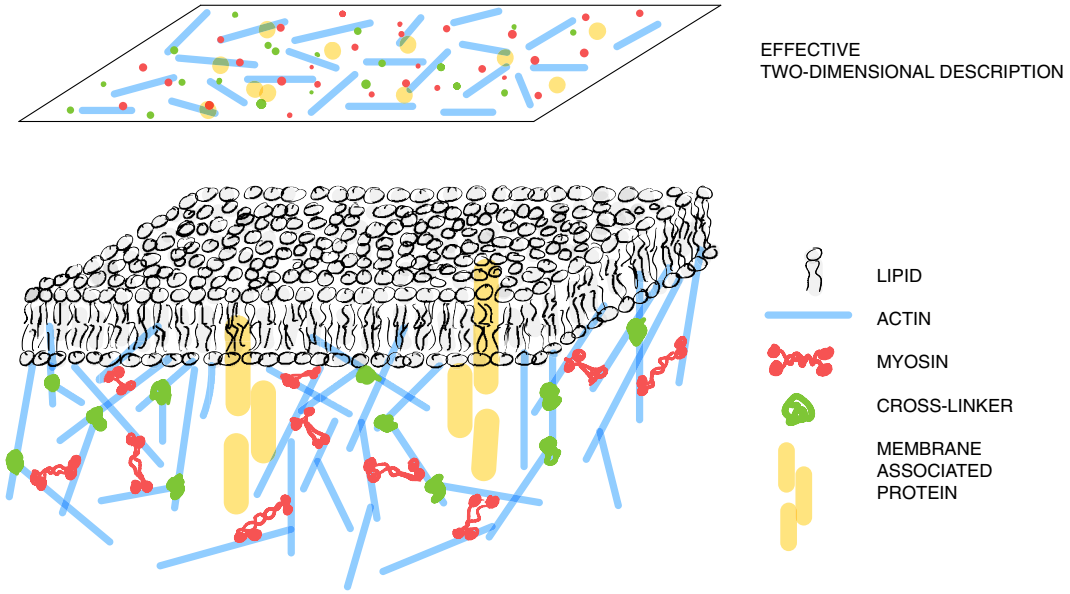

Figure 1: The actomyosin cortex is quasi two-dimensional polymeric meshwork of actin filaments located under the plasma membrane, and interspersed in this cortical meshwork are myosin motors, cross-linkers and membrane-bound proteins. Actin filaments are oriented, on the average, in a direction normal to the local plane of the cortex. The in-plane components of the actin filaments can be described by a polarity field **p**. Averaging over the thickness of the cortex, an effective two-dimensional active hydrodynamic theory for the in-plane components of the actin filaments can be developed. Large-scale flows generated in this two-dimensional layer can generate density and orientation patterns, and also affect the transport of embedded proteins.

It should be noted that unlike an incompressible three-dimensional active polar gel, the two-dimensional velocity field **v** can have regions of nonzero divergence, and these regions correspond to the locations where material can leave the plane of the cortex into third dimension. The stresses arising from orientation fields and active processes depend on the nature of the local ordering of actin filaments.

For a polar active gel, with a polarity order parameter **p**, the corresponding stresses are

$$\boldsymbol{\sigma}_{\mathrm{o}} = \nu\left(\mathbf{p}\otimes\mathbf{h}+\mathbf{h}\otimes\mathbf{p}-[\mathbf{p}\cdot\mathbf{h}]\mathbb{I}\right)+\overline{\nu}\,[\mathbf{p}\cdot\mathbf{h}]\mathbb{I} \tag{8}$$

$$\boldsymbol{\sigma}_{\mathrm{a}} = \zeta\,\Delta\mu\,\mathbb{I}+\overline{\zeta}\,\Delta\mu\left(\mathbf{p}\otimes\mathbf{p}-\frac{1}{2}[\mathbf{p}\cdot\mathbf{p}]\,\mathbb{I}\right) \tag{9}$$

where $\otimes$ represents the outer product, ν and $\overline{\nu}$ are alignment parameters, and $\Delta\mu$ represents the chemical potential difference of a mechanochemical force-generating reaction, for instance the hydrolysis of ATP. The activity coefficients, ζ and $\overline{\zeta}$ are functions of those n_i that regulate active force generation, for instance the number density of myosin motors. The molecular field conjugate to the polarity $\mathbf{h} = -\delta F/\delta\mathbf{p}$ is the functional derivative of a free-energy such as the Landau-de Gennes free energy for polar liquid crystals[63]. The time evolution of the polar order parameter is given by

$$\begin{aligned}\frac{D\mathbf{p}}{Dt} = \frac{\mathbf{h}}{\gamma} &- \nu\,\boldsymbol{\epsilon}\cdot\mathbf{p}-\overline{\nu}\,\mathrm{Tr}(\boldsymbol{\epsilon})\,\mathbf{p}\\ &+\lambda_0\,\mathbf{p}-\lambda_1\,(\nabla\cdot\mathbf{p})\,\mathbf{p}\\ &-\lambda_2\,(\mathbf{p}\cdot\nabla)\mathbf{p}-\lambda_3\,\nabla(\mathbf{p}\cdot\mathbf{p})\end{aligned} \tag{10}$$

where γ is a kinetic coefficient. The terms containing the λ_i are a result of active processes, and are not allowed for a system at thermodynamic equilibrium. An important point to note that one cannot have an isotropic active stress in three-dimensions. However, for the thin film approximation of the cortex that we are considering here, with actin filaments oriented, on the average, in a direction normal to the plane of the cortex, an in-plane isotropic active stress is allowed.

If the in-plane components of the actin filaments do not have a net polarity, but are nevertheless aligned along an axis, then an appropriate hydrodynamic description is that of an active nematic gel, with a second-rank tensor

$\mathbf{Q}$ as the order parameter. The contribution to the stresses are then

$$\boldsymbol{\sigma}_{\mathrm{o}} = -\beta \frac{\delta F}{\delta \mathbf{Q}}, \tag{11}$$

$$\boldsymbol{\sigma}_{\mathrm{a}} = \xi\, \Delta\mu\, \mathbb{I} + \bar{\xi}\, \Delta\mu\, \mathbf{Q}, \tag{12}$$

where β is an Onsager coefficient, while ξ and $\bar{\xi}$ are activity coefficients that can be regulated by the number densities of molecular motors. The nematic order parameter evolves according to

$$\frac{D\mathbf{Q}}{Dt} = -\frac{1}{\Gamma}\frac{\delta F}{\delta \mathbf{Q}} + \lambda\, \mathbf{Q} - \beta \left[\boldsymbol{\epsilon} - \frac{\mathrm{Tr}(\boldsymbol{\epsilon})}{2}\, \mathbb{I}\right], \tag{13}$$

where Γ is a kinetic coefficient and the term containing λ is a result of active processes.

The hydrodynamic equations discussed above provide a closed set of equations for the density, flow and orientation fields of the cortex. For instance, in the case of an active polar fluid, Eqs. (1)–(4) and (7)–(10) govern the spatiotemporal evolution of the number-density fields n_i, the hydrodynamic velocity field $\mathbf{v}$ and the polarity field $\mathbf{p}$. These equations must be supplemented with appropriate boundary conditions. In addition, external non-autonomous signals, arising from other signaling processes, for instance, can be included in the reaction terms R_i or in the spatiotemporal regulation of the active stresses. As remarked earlier, the active stresses are regulated by the number-density fields of molecular motors. An often used functional form for active-stress regulation is

$$\zeta\, \Delta\mu = (\zeta\, \Delta\mu)_0\, \frac{n_{\mathrm{m}}}{n_{\mathrm{m}} + n_*}, \tag{14}$$

where n_{m} is the number-density field of myosin motors, $(\zeta\, \Delta\mu)_0$ is a bare active-stress and n_* is a saturating density. Note that in the hydrodynamic equations presented above, we have assumed that there is a constant and perennial supply of ATP around for the action of motors and filaments and, as such, have not explicitly considered the dynamics of these high energy molecules.

In the discussion above, we have implicitly neglected the chirality of the cortex, and have only considered symmetric stress tensors. The cortex, however, is a chiral active material. Actin filaments are chiral structures and, thus, active process not only generate forces and but also generate torques. The most important change to the above equations, in addition to considering torque balance, is the inclusion of an antisymmetric active stress[64–66]. Active chiral processes have been observed at the cellular level[67,68], and even have implications for lineage specification at the organismal level[69]. However, the most fundamental aspect where active torques are bound to play a crucial role is in the establishment of the left–right axes of developing embryos[70,71].

It should be noted that other (higher order) terms permitted by symmetry are allowed in the hydrodynamic equations. For instance, the transport equations for the n_i can have an additional flux term proportional to the local polarity $\mathbf{p}$. We have also not worried about permeation effects and have assumed a one-component description of the active gel. Elastic effects acquire significance when the cortex behaves like an active elastomer[72], and other effects such as coupling to the cytoplasmic flows and membrane elasticity can become important in different situations. The justification for retaining certain terms, or neglecting others, in the hydrodynamic equations is dependent on the context and experimentally measurable quantities.

Many of the kinetic parameters that appear in the hydrodynamic equations, such as the coefficients of diffusion D_i, the viscosities η and η_b, and the flow alignment parameters ν and ν_b, are emergent properties of the active material at this level of description. The values of the parameters, though controlled by gene regulation patterns, cannot be calculated easily from microscopic pictures. However, their values can be inferred from experiments designed to measure the relevant hydrodynamic fields[32,73–79], and, as such, a consistent description of the cortex can be built at this coarse-grained level. In other words, these mesoscopic emergent features should really be thought of phenotypic parameters that represent the state of the cortex at this coarse-grained level and are experimentally accessible.

4 Cellular Processes Driven by the Actomyosin Cortex

The actomyosin cortex is directly responsible for driving several cellular processes. We now discuss a few of these processes and, where possible, also point out the way in which hydrodynamic models have been used to understand them.

4.1 Mechanochemical Patterns

The equations of active hydrodynamics outlined above have many pattern forming instabilities. These emergent nonequilibrium phases arise form a subtle interplay between mechanochemical force-generation, fluid flow and orientational ordering. Put simply, a homogeneous state of the

cortex can get de-stabilized when hydrodynamic flows arising from active stresses can overcome the effects of homogenizing processes such as diffusion.

A very simple example of such an active pattern formation process can be illustrated by considering an isotropic active fluid with a single chemical regulator of the mechanical stress[80]. The resulting equations, in one dimension, for the number density of motors $n_{\rm m}$ and the hydrodynamic flow v, are

$$\partial_t n_{\rm m} = -\partial_x(v\, n_{\rm m}) + D\,\partial_x^2 n_{\rm m} - \kappa\,(n_{\rm m} - \overline{n}), \tag{15}$$

$$\eta_b \partial_x^2 v - \alpha\, v = -\partial_x(\zeta\,\Delta\mu), \tag{16}$$

where we have considered a simple linear turnover reaction (with rate κ and a reference density $\overline{n}$) along with a frictional approximation for the external forces on the active fluid. The active stress $\zeta\,\Delta\mu$ is regulated by the density of myosin motors as in Eq. (14). When active contractile flows overcome the homogenizing effects of diffusion, i.e., when, say, $(\zeta\,\Delta\mu)_0 \gg \alpha D$, the state with uniform density (and zero velocity) is unstable to small perturbations, and leads to the emergence of periodic patterns in both $n_{\rm m}$ and v. With two regulators of the active stress, the above equations leads to the emergence of spontaneous pulsatile patterns[81] that could underlie the oscillatory patterns of myosin motors seen in many experiments[72,75]. Note that the mechanism of pattern formation exhibited by these equations are not the well-understood diffusion-driven instabilities found in classical reaction-diffusion systems that underlie Turing patterns. Active mechanochemical patterns involve mechanical forces in an essential and inseparable manner. For instance, without active stresses, Eqs. (15) and (16) do not have any non-trivial patterns. It is important to emphasize that these active mechanochemical patterns represent a new class of pattern forming systems and form the next logical steps in incorporating mechanical forces into morphogenetic patterns[82].

With the inclusion of orientational effects, the active hydrodynamic equations for the actomyosin cortex lead to a much richer variety of patterns such as emergent "quasi-particles" comprised of motile defects with very interesting effective interactions[83] and fluctuation dominated phase-ordering mechanisms[84]. A very important case is the coupling of cortical flows and polarity patterns to GPI-anchored proteins in the cell membrane leading to the emergence of non-trivial functional nanoclusters of these proteins[85–87]. This picture of an active composite cell surface, wherein the patterning of membrane associated proteins is largely driven by polar patterns in the underlying actomyosin cortex, is a prime example of the possible ways in which active processes can control cellular patterns.

4.2 Cell Division

Actomyosin cortical flows have long been speculated to drive cell division and cell polarity patterns[17]. The formation of an actomyosin contractile ring during cell division can be explained within the framework of an active nematic gel description[88]. A myosin gradient generates hydrodynamic flows that align the actin filaments into a ring-like geometry which further undergoes a contraction to cleave the cell. Such hydrodynamic flow induced couplings to orientation fields of actin filaments can be measured experimentally. In fact, a hydrodynamic theory along the lines of Eq. (13), can quantitatively account for the spatial profiles of the nematic order parameter $\mathbf{Q}$ in the zygotes of *Caenorhabditis elegans*[89] using measured flow compression rates. This highlights the importance of hydrodynamic flows in organizing cell division patterns.

Simple models of cortical flow patterns, analogous to Eqs. (15) and (16), but on a curved surface, coupled to the cytoplasm modeled as a viscous Newtonian fluid can account for both cell polarity patterns and cell division patterns[90]. Furthermore, coupling hydrodynamic flows to contracting rings could possibly explain asymmetric ingression of cytokinetic furrows[91].

Active processes in the cortex not only generate patterns on the cell surface but also interact strongly with various cytoplasmic components in the cell. For instance, the positioning of the mitotic spindle in a dividing cell is tightly controlled by the interactions of microtubules with the actomyosin cortex[73,92]. Simple models of such microtubule-cortex interactions lead to an explanation of the observed oscillations in the mitotic spindle[93]. Recent work shows that the chirality of the cortex can control the spindle skew and cell reorientation during lineage specification[69].

It is interesting to note that several of the major unanswered questions about cytokinesis involve the actomyosin cortex[94,95] and possible answers to these questions will probably arise from a system level, i.e., coarse-grained, description rather than detailed molecular studies[96].

4.3 Cell Polarity

It has long been observed that mechanical flows in the actomyosin cortex are strongly connected to the establishment of cell polarity in the *C. elegans* zygote[97,98]. A pioneering work quantitatively measured these flows, showed that they are driven by gradients in actomyosin contractility, and that an active hydrodynamic theory of the cortex, akin to Eq. (16), can quantitatively account for these flows given a myosin profile[74]. How do these hydrodynamic flows drive the establishment of a polarity pattern? Transport equations for the surface densities of polarity proteins, using the experimentally measured hydrodynamic flows, qualitatively accounted for the polarity patterns[99].

How do we develop a physical and consistent description of cell polarity patterns that couple to the active mechanics of the cortex? Polarization of the *C. elegans* zygote is achieved through the asymmetric distribution of partitioning defective (PAR) proteins on the cellular surface. In this patterning process, the segregation of anterior and posterior PAR complexes, with mutually antagonistic interactions amongst each other, to either side of the embryo also establishes the anteroposterior axes of the embryo. The evolution equations for the surface densities of the anterior PAR complex n_{a}, the posterior PAR complex n_{p} and that of the non-muscle myosin motors n_{m} satisfy

$$\partial_t n_i = -\partial_x(v\, n_i) + D_i \partial_x^2 n_i + R_i(n_{\mathrm{a}}, n_{\mathrm{p}}, n_{\mathrm{m}}) + S_i(x,t), \tag{17}$$

for $i \in \{\mathrm{a,p,m}\}$ and where x represents the position coordinate along the anteroposterior axis in a one-dimensional description of the system[100]. The hydrodynamic flow v is obtained from Eq. (16). These equations, with appropriate chemical reactions R_i, allow for the stable co-existence of both uniform and domain states in certain regions of the parameter phase-space, with a finite sized perturbation required for transitioning from one state to the other. The polarity process, then, is one of starting from a uniform state and transitioning into a domain state to establish a polar pattern of PAR proteins on the cell surface. This transition is triggered by the external source terms $S_i(x,t)$ whose origin, and spatiotemporal profiles, are governed by certain upstream developmental signals. The recent work[100] studied this system in detail, with a careful measurement of surface concentrations and flow fields, and showed a quantitative match between the experimental profiles of $n_i(x,t)$ and $v(x,\, t)$, and the theoretical predictions of Eqs. (16) and (17).

An important conceptual point exemplified by the theory and experiments in[100] is that of guided self-organization. The cell polarity system described by Eqs. (16) and (17) leads to a self-organized system that has both uniform and polarized states stably coexisting in the same region of parameter space. Hence, this system behaves as a switchable module with stable spatial patterns (uniform and polarized) as the two states. The "guides" represented by the source terms $S_i(x,t)$ toggle the state of this switch in a spatiotemporally controlled manner. One of the sources locally reduces actomyosin contractility at the future posterior pole of the embryo, and triggers large-scale cortical flows that then push the system away from the uniform state, and into the basin-of-attraction of the polarized state, whereupon the self-organized dynamics of the system then ensures that a polarity pattern reliably emerges. Thus, this mechanochemical cell polarity pattern is an example of a self-organized system guided by signals to transition from one stable state to another. Hydrodynamical flows in the actomyosin cortex constitute one of these guiding signals.

The cortical flows driven by active processes on the cellular surface can drive cytoplasmic flows as well[101,102]. In fact, recent work has shown the coupling between surface mechanics and intracellular cytoplasmic flows can also affect the establishment of the cell polarity patterns discussed above[103].

4.4 Cell Motility

Early studies of fish keratocytes showed that their motility is largely governed by lamellipodial protrusions of the membrane driven by actomyosin networks[27,28]. The preferential polymerization of actin filaments at the leading edge of the cell and the accompanying de-polymerization at the trailing edge generates a retrograde flow in the cell. Hydrodynamic theories of active polar gels have shown that, in such a scenario, contractile stresses generated at the leading-edge can lead to a net motility of cells crawling on a substrate[104]. Such contractility-mediated mechanisms can also lead to cell migration in three-dimensional environments[105], such as in the migration of amoeboids[106] where active gel models have also been used to account for their motility[107].

Migration without lamellipodia is also possible. In many cases, blebs in the actomyosin cortex are implicated for this kind of motility[108,109]. Blebs are localized regions of the membrane that transiently detach from the actomyosin cortex.

The membrane protrusion, driven by cytoplasmic pressure, can then advance the cell surface in the direction of the bleb. The finite timescale required for the turnover process of the actomyosin cortex to "heal" this wound make blebs an excitable phenomenon. Physical models for bleb formation, their size, shape, and the dynamics of traveling blebs have shown that this unusual dynamics of the membrane-cortex coupling is also a possible route for cell motility[110–112].

4.5 In Vitro Reconstitution of the Actomyosin Cortex

In the previous sections, we have discussed important examples of cellular processes driven by actomyosin activity. In vivo studies, though physiologically relevant, are hard to control. As such, several studies have focussed attention to reconstitute in vitro biomimetic models of the actomyosin cortex. These include correlation and response measurements of three-dimensional cross-linked networks of actin filaments containing myosin motors and ATP[113], systems consisting of purified actin and myosin proteins that demonstrated the formation of contractile actin structures[114], and the actin flows observed in cytoplasmic extracts of *Xenopus* eggs in cell-sized 'water-in-oil' droplets[115–117]. This last system also displays long-ranged flows in sparsely cross-linked networks and structural symmetry breaking in the case of high cross-linker density arising from self-organized stress patterns[118].

Gliding motility assays constitute an important way to mimic the cortex in the lab. In these studies, a carpet of myosin motors is fixed on a substrate on which actin filaments can easily glide[119,120]. Being on a substrate, these systems lack momentum conservation and hence do not need force-balance considerations. Nevertheless, gliding motility assays have uncovered a wealth of patterns in polar active systems, including clusters and swirls, coexistence of ordered states with polar and nematic symmetry, and collective flocking states of actin filaments.

Developing in vitro systems of the actomyosin cortex along with a realistic coupling to the plasma membrane is an experimental challenge. Earlier studies tried to nucleate actin polymerization in the inner membranes of liposomes[121]. An important development in this direction has been to reconstitute a lipid bilayer system along with a thin layer of the actomyosin cortex attached to it via membrane-associated actin-binding proteins[122]. Active stresses generated from the hydrolysis of ATP can lead to the emergence of actin bundles and polar asters of actin filaments depending on the density and the length of actin filaments, and motor concentration. Membrane associated proteins are seen to be advected by cortical flows and self-organize into transient clusters. This study paves the way for further exploration of cell surface patterns driven by an inextricable link between the actomyosin cortex and the plasma-membrane.

5 Shaping Cells and Tissues Using Actomyosin Contractility

In multicellular organisms, collections of cells form tissues and organs. These assemblies show self-organized patterns and undergo large deformations to sculpt the organism, particularly during the developmental phases. Understanding the emergence of the three dimensional form in developing embryos is a big challenge in science, and it has long been speculated that physical and chemical forces must be intricately involved in this process[123]. It is only in recent decades that we are beginning to uncover the full extent of the physical processes involved in building tissues and organs from cells.

Tissue patterns that involve mechanochemical forces are mediated, to a large extent, by the cellular cytoskeleton, and the primary player is the actomyosin cortex of cells [124–126]. At this larger scale of tissue morphogenesis, entire cells act as the active force-generating units. Not surprisingly, the hydrodynamic theory of active gels that we discussed in Sect. 3, which was originally developed for describing the dynamics of density, flow and orientation fields in the actin cortex, can be adapted to describe the dynamics of many tissues, such as epithelial monolayers[127–129]. The density fields here are those of cells and tissue turnover is maintained by a fine-balance between cell-division and death. Cellular polarity, either in cell shape or in the asymmetric distribution of proteins, can play the role of orientation fields. As such, similar hydrodynamic descriptions, with appropriate modifications, are applicable to tissues as well. However, the relevant length and time-scales are expanded leading to, for instance, a shift in the observed mechanical responses. For example, elastic effects become much more significant as the viscoelastic stress relaxation timescales are quite long.

5.1 Tissues: In Vivo and In Silico

Coordinated activity of actomyosin cortices across many cells can drive large-scale tissue

morphogenesis. This is possible since the actin cortices of neighboring cells can get coupled[130]. The extension of the germband tissue during the embryogenesis of the fruit-fly *Drosophila melanogaster* is a well studied example of large scale tissue morphogenesis driven by actomyosin activity. The remodeling of epithelial cell junctions driven by planar polarized actomyosin flows[131], anisotropic growth of junctions leading to large-scale tissue deformations[132], and pulsatile patterns of actomyosin contractility that control junction lengths in an anisotropic manner[133], have all been directly linked to mechanical force-generation mechanisms in actin filaments and myosin motors.

Another prominent example of a well-studied system is the wing-blade of *D. melanogaster*[134]. The wing-blade is shaped by a combination of cell division, cell rearrangement and cell shape change events, along with a coupling to the surrounding extracellular matrix that provides boundary conditions for the deformations. A coarse-grained theory, that treats cell densities, area, elongation and structural anisotropies as the hydrodynamic variables, shows that hydrodynamic flows can explain the active rheological properties of tissues in general, and the wing-blade in particular[135]. This theory closely resembles the active nematic gel equations that we outlined in Sect. 3.

At a larger scale, the contractile nature of the actomyosin cortex manifests itself in the constriction of supra-cellular structures. For instance, during zebrafish gastrulation, the enveloping cell layer spreads over the underlying yolk with the forces required for this process being provided by the constriction of an actomyosin ring which also acts like a flow-friction motor[136]. Supracellular actin cables, like those observed during the dorsal closure of *D. melanogaster*[137], can be seen to arise from pattern forming instabilities in active gels[129,138]. Such large-scale emergent structures have also been reported in the extra-embryonic epiboly of the insect *Tribolium castaneum*[139,140].

A laboratory imitation of epithelial tissues studies spreading monolayers of cultured cells on either homogeneous or patterned substrates. The collective dynamics of these spreading cells have been very instructive in deciphering cell communication strategies and to act as model systems for wound healing[141,142]. Here too, the motility of cells is driven by actin protrusions in so-called "leader-cells" at the edge of the spreading layer. Theories of mechanochemical patterns in spreading monolayers have uncovered fascinating patterns, coupling cell locations with their size and the expression levels of certain signaling proteins that eventually control mechanical properties via the actomyosin cortex[143]. Recent studies have shown that monolayers of cultured epithelial cells can transition from a two-dimensional geometry to that of a three-dimensional spheroidal aggregate, and that this is driven by actomyosin contractility and adhesion forces (between cells and with the substrate). An appropriate hydrodynamic theory of an active polar gel explains this behavior in terms of a novel wetting transition driven by the competition between cell contractility and traction forces[144].

In addition to the hydrodynamical models discussed above, epithelial tissues have been successfully modeled by vertex models. In this approach, cells are modeled as polygons with an elastic energy functional that governs their deformations[145,146]. With A_α and P_α denoting the area and perimeter of the αth cell, and l_{ij} denoting the edge of the bond connecting the vertices i and j, this energy functional is

$$E = \sum_{\alpha \in \text{cells}} \left[\frac{K_\alpha}{2} \left(A_\alpha - \overline{A}_\alpha \right)^2 + \frac{\Gamma_\alpha}{2} P_\alpha^2 \right] + \sum_{i,j \in \text{bonds}} \Lambda_{ij} \, l_{ij}, \tag{18}$$

where K_α is an area elastic modulus that penalizes area fluctuations around the preferred value $\overline{A}_\alpha$, Γ_α is a perimeter coefficient and Λ_{ij} is a bond-tension parameter. The area elasticity arises from conservation of cell volume, while the perimeter and line-tension terms, represented by the parameters Γ_α and Λ_{ij} respectively, arise from actomyosin contractility. Minimum energy configurations can either be arrived at by Monte-Carlo simulations or by a dissipative first-order dynamics for the vertices $\dot{\mathbf{r}}_i = -\partial E / \partial \mathbf{r}_i$. Furthermore, cell division and topological rearrangements of cell junctions can easily be incorporated into vertex models. These approaches have also been generalized to three dimensions in recent years and provide valuable pictures of the three-dimensional morphology of epithelial sheets[147–149]. Addition of active polar forces on vertices to mimic motile cells is also possible within this framework.

5.2 Geometrodynamics of Active Matter

Theoretical models of the actomyosin cortex modeled as an active gel are usually studied on fixed geometries. However, the stresses and flows that arise in active surface patterns can naturally drive geometrical deformations of the underlying manifold. The most fundamental example is, of course,

cell division. Actomyosin contractility not only drives the formation of the cytokinetic ring, but also constricts it and, in the process, changes the shape of the cell. The changed cell shape will, in turn, affect the surface patterns. Thus, the coupling between patterns (in density, flow, orientation, stress fields) and the underlying shape naturally leads to a geometrodynamics of active matter. This brings in a completely new perspective into the consequences of actomyosin activity. Morphogenetic patterns in cells and tissues result from the tight couplings that exist between gene expression patterns, mechanical forces generated (primarily) in the cytoskeleton, and the changing geometry. It is thus natural that generic hydrodynamic descriptions of active matter should incorporate dynamical geometries into their framework. This, however, is a challenging task since the mathematical formalisms required are non-trivial. Nevertheless, several recent studies have broached this hard frontier[90,138,150–158].

The first task in the formulation of a geometrodynamics of active matter is to recast the hydrodynamic equations of active gels, for instance Eqs. (1)–(4) and (7)–(10), into a form appropriate for a curved, but stationary, manifold. For scalar fields, this is rather straightforward. For vector and tensor fields (such as flows **v**, polarity **p** and nematic order parameters **Q**), this, however, is a non-trivial task. The resulting hydrodynamic equations involve couplings of the tensor fields with the geometrical descriptors of shape, such as the curvature tensor, and are not amenable to analytical solutions, except for shapes with high symmetry (such as a sphere). Numerical methods are thus inevitable, and recent studies are uncovering a plethora of new active patterns that can sense and respond to surface geometry. The next step towards a dynamical geometry would be to formulate the equations of motion for the metric tensor and the curvature tensor[158].

The difficulties inherent to active matter theories with dynamical geometries discussed above makes one wonder if they are useful to understand biological patterns. To see that this must be so, one only has to realize that morphogenetic patterns seen in developing embryos are not just patterns of gene expressions, but are also dynamical shape patterns. Thus, the generation of form will naturally involve geometric patterns[123]. To emphasize this point, consider, as an example, recent studies on *Hydra* regeneration[159,160]. The emergence of the three-dimensional shape of a *Hydra* is shown to be tightly correlated with the pattern of topological defects in the orientation of actin filaments. As such, geometry is bound to be a dynamical variable and must be included in theories concerned with developing embryos.

6 Outlook

In this brief review, we began by discussing the structure and functions of the actomyosin cortex. We next turned to the mechanisms of active force-generation and the important role played by nonlinear elasticity in leading to actomyosin contractility. After an overview of various theoretical approaches to study the cortex, we presented a simplified summary of the hydrodynamic equations for an active polar gel. Here, we highlighted the various active terms that arise in the equations for density, flow and orientation fields, and how their strengths can be regulated by molecular motors. We then discussed mechanochemical patterns that are a natural result of the hydrodynamic theory. Specifically, we discussed patterns seen during cell division, cell polarity establishment and cell motility as archetypal examples of these novel mechanochemical pattern forming mechanisms. Next, we discussed the role of actomyosin contractility in driving large-scale patterns at the level of entire tissues. The examples of the germ-band and the wing-blade in *D. melanogaster* embryos served to emphasize the role of active processes in controlling tissue level patterns. After a brief discussion of vertex models, we sketched the open-ended and nascent field of studying the geometrodynamics of active matter within the hydrodynamical approach.

Are mechanical forces essential to understand cell and developmental processes? The answer is definite yes[161]. However, mechanics alone cannot sculpt cells and tissues into functional organs and organisms. What is needed is an understanding of the novel physical principles that direct information flow from gene expression patterns, via cytoskeletal mechanics, into patterning cells and tissues. How this achieved in living organisms is far from clear.

As we discussed earlier, the hydrodynamic method averages over microscopic details of the stochasticity inherent in chemical reactions and develops coarse-grained effective descriptions valid at length and time scales that are large compared to the molecular level. Thus, the hydrodynamic method is an intermediate "phenotypic level" description that is amenable to mathematical modeling and hence has predictive power. The various examples that we discussed in this review, both at the cellular and tissue level, where this approach has been successfully applied, demonstrate both its vast potential and generality.

Moreover, coupled with careful experimental measurements of the macroscopic and emergent properties (like viscosity, friction, active stresses, flow-alignment parameters), one can build a coarse-grained and consistent picture at this level, without recourse to genetic details at every possible turn. This is supported by the many observed morphogenetic redundancies in the cortex. The mesoscopic properties of the actomyosin cortex are controlled by many genes[162,] and this makes a case for condensed matter like emergent descriptions to be really useful.

The mechanics of the cellular actomyosin cortex, coupled with biochemical signaling, is the primary interface between gene expression patterns and the emergent morphology of cells and tissues. We believe that a significant amount of work is required to uncover the possible phenomenon at this fascinating intersection of biochemical networks, mechanics of force generation and the geometry of shape in cells and tissues, and this will occupy researchers for some time.

Publisher's Note

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K. Vijay Kumar is on the faculty of the International Centre for Theoretical Sciences (ICTS-TIFR) of the Tata Institute of Fundamental Research, Bengaluru. He has a PhD in physics from the Indian Institute of Science (IISc), Bengaluru. He spent a few years as a postdoc at the Max-Planck-Institute of Physics of Complex Systems and the Max-Planck-Institutes for Molecular Cell Biology & Genetics in Dresden, Germany. His research interests are broadly in the physics of living systems with the current focus on understanding mechanochemical processes during morphogenesis.