nature physics

INSIGHT | PROGRESS ARTICLES

PUBLISHED ONLINE: 3 FEBRUARY 2015 | DOI: 10.1038/NPHYS3224

Active gel physics

J. Prost[1,2], F. Jülicher[3]* and J-F. Joanny[1,4]

The mechanical behaviour of cells is largely controlled by a structure that is fundamentally out of thermodynamic equilibrium: a network of crosslinked filaments subjected to the action of energy-transducing molecular motors. The study of this kind of active system was absent from conventional physics and there was a need for both new theories and new experiments. The field that has emerged in recent years to fill this gap is underpinned by a theory that takes into account the transduction of chemical energy on the molecular scale. This formalism has advanced our understanding of living systems, but it has also had an impact on research in physics *per se*. Here, we describe this developing field, its relevance to biology, the novelty it conveys to other areas of physics and some of the challenges in store for the future of active gel physics.

One of the distinctive properties of living systems is their faculty to move, change shape, divide and create their own morphology. Cells are the elementary building blocks of living systems. Even seemingly simple prokaryotic single-celled organisms such as bacteria exhibit an astonishing complexity. However, things are even richer when we look at multicellular eukaryotic organisms, particularly those in the animal world. Their cells are extraordinarily dynamic, flexible in shape, and can perform an amazing number of functions[1]. For a physicist, they are both a fascinating and a frightening object: the number of variables that is necessary to describe their varied behaviours is well above the number of genes if one includes phospholipids, non-coding DNA and post-translational modifications[1].

Fortunately, after a century of skilled experimental work, a certain simplicity has begun to emerge. Key mechanical properties of cells are controlled by a biopolymeric system, called the cytoskeleton. It is based on three types of protein filaments: intermediate filaments, microtubules and actin filaments[1]. The mechanical contribution of intermediate filaments is thought to take place mainly at large deformations and over long times, and is passive[2,3]. Its description involves semi-flexible polymer physics close to equilibrium[4]. But microtubules and actin filaments are fairly rigid linear structures, which are fundamentally out of equilibrium. Furthermore, they are structurally polar and provide a directionality for active processes. They continuously hydrolyse ATP or GTP (adenosine triphosphate and guanosine triphosphate, respectively) into ADP or GDP (adenosine diphosphate and guanosine diphosphate, respectively) and inorganic phosphate. As a result, at steady state they have the capacity to polymerize at one end of the filament and depolymerize at the other end. This process, known as treadmilling, occurs under physiological conditions, and plays an important role in cell motility, cell signalling and mitotic spindle assembly[1].

Cytoskeletal filaments have another important characteristic: they can act as tracks to energy-transducing proteins called molecular motors, which can ride along them. Three superfamilies of motors can be distinguished: myosins move on actin filaments, whereas kinesins and dyneins move on microtubules[1]. In turn, the motors can move the cytoskeletal filaments if they are anchored on a substrate or on a crosslinked structure such as a gel. Most of the mechanical properties of animal cells are controlled by a thin layer of the actin–myosin meshwork (a few hundred nanometres to micrometres thick) called the cell cortex[5] (Fig. 1). It is a dense gel with a mesh size of a few tens of nanometres. At first sight, it can be considered as a physical gel because the actin filaments are crosslinked by proteins having a finite bound time. The treadmilling phenomenon and the action of myosins, however, introduce fundamentally novel aspects to the system, particularly local breaking of detailed balance. So what is the new emerging physics in such active gels?

From the point of view of symmetry, these systems lack time-reversal symmetry, because energy is constantly transduced. Furthermore, they can acquire orientational order as the constituents are polar filaments. We define active gels as soft materials in which detailed balance is broken locally. They are members of the larger family of active systems, recently reviewed in ref. 6. Note that active gels are different from those at work in the mechanochemical engines invented by Aharon Katchalsky and colleagues, which are locally passive gels obeying detailed balance that are driven on large scales by two different external baths[7]. The most spectacular property of active systems is their capacity to spontaneously move, but they exhibit many other fascinating features. Note that, in general, active systems include herds, bird flocks, fish shoals and bacterial colonies, as well as non-biological examples such as vibrated granular systems, collections of self-propelled particles and crowds of interacting robots.

Constructing the active gel theory

The challenge is to construct a theory, keeping track of the fact that one is dealing with a system of filaments that are crosslinked over finite periods of time and redistributed by the action of molecular motors. One has first to identify slow variables relevant for a macroscopic or mesoscopic description. These are given by conserved quantities and continuous broken symmetries provided that we consider phenomena occurring at length scales large compared to molecular scales, here given by the gel mesh size[8]. Clearly, overall mass, solvent mass, energy and momentum are conserved and, on timescales short compared to production and degradation rates, we can consider the number of actin monomers and motors to be conserved. In the following we consider isothermal systems; thus we can ignore energy conservation.

When the filaments are on average parallel to each other, either with nematic or polar order, one must add either a director or

[1]Physicochimie Curie (Institut Curie/CNRS-UMR168/UPMC), PSL Research University, Institut Curie, Centre de Recherche, 26 rue d'Ulm, 75248 Paris Cedex 05, France. [2]Mechanobiology Institute, National University of Singapore, 5A Engineering Drive 1, Singapore 117411, Singapore. [3]Max-Planck-Institute for the Physics of Complex Systems, Nöthnitzer Str. 38, 01187 Dresden, Germany. [4]E.S.P.C.I-ParisTech, 10 rue Vauquelin, 75231 Paris Cedex 05, France. *e-mail: julicher@pks.mpg.de

NATURE PHYSICS DOI: 10.1038/NPHYS3224

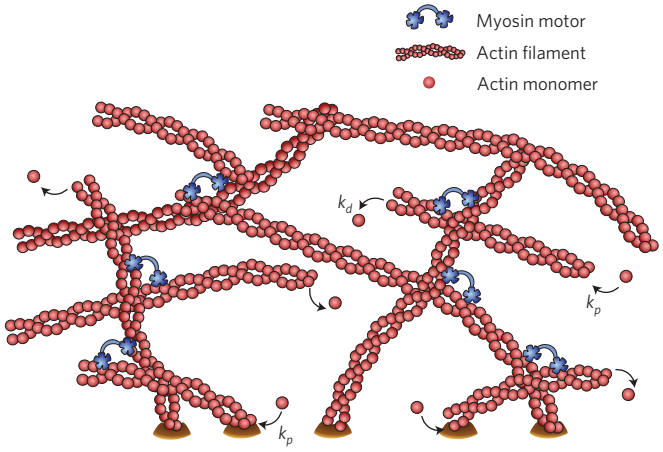

Figure 1 | Illustration of an active gel consisting of actin filaments, myosin motors and passive crosslinks (not shown). Filament polymerization and depolymerization processes are indicated by the rates k_p and k_d.

a vector field as a slow variable. From there, several approaches may be chosen. The simplest approach, first used to describe active nematics, considers small perturbations with weak gradients (long wavelengths), keeping all lowest-order terms allowed by symmetry in the perturbation and in the gradient expansion[9,10]. Because the system is out of equilibrium, no relation exists between the coefficients involved in the expansion. This is a very efficient and general way of writing equations. The only concern is that one has to assume the existence of the state around which the system is perturbed although its existence is not guaranteed.

A second approach is to perturb the system in the vicinity of an equilibrium state. This guarantees the existence of the reference state and allows one to use the formalism of out-of-equilibrium thermodynamics and Onsager symmetry relations[11,12]. It also permits one, in this limit, to clearly identify dissipative and reactive terms, generalized forces and fluxes. In particular, one has to explicitly introduce the generalized force that drives the system out of equilibrium. For the cytoskeleton, because we know the free energy source is the ATP (or GTP) hydrolysis, the natural choice of generalized force is the difference $\Delta\mu = \mu_{\mathrm{ATP}} - (\mu_{\mathrm{ADP}} + \mu_{\mathrm{Pi}})$ between the chemical potential of ATP and that of the hydrolysis products ADP and inorganic phosphate Pi. The flux conjugate to this force is the reaction rate of the ATP hydrolysis. The procedure is well controlled, but the range of validity of the theory is limited to small chemical potential differences for which the response is linear. The small chemical potential difference is a real limitation because the chemical potential difference under physiological conditions is of the order of $20\,kT$ (where k is Boltzmann's constant and T is the temperature) and may thus not be considered small. This procedure also allows us to describe in a unique formulation the short-time elastic behaviour and the long-time active liquid crystal behaviour, provided that the crossover time between short and long times is long compared to microscopic times. This is the case in the actin–myosin system, as it is typically of the order of a few tens of seconds. Note also that the crossover might be more complex in view of the non-trivial frequency dependence of the loss and storage moduli of passive actin gels[4].

A third approach consists in developing a microscopic theory, which in principle can describe all length and time scales. In fact, for the theory to be tractable, one has to assume low actin and motor densities and consider the long-time limit[13–15]. The main feature of all three approaches is that the constitutive relation between stress and generalized forces has a new term, which does not derive from a potential and can describe either a contractile or an extensile behaviour: it is known as 'active stress' (Box 1, equations (1) and (2)). This term can be obtained by coarse-graining a microscopic description in which individual elements are represented by force dipoles[9,10]. The resulting macroscopic active stress is the average force dipole density. In a system with nematic symmetry the anisotropic part of the active stress is the most important new term compared to a passive system. In a situation where the total anisotropic stress can be maintained at zero by appropriate boundary conditions, this term generates a spontaneous shear at short times and a shear rate at long times (Box 1, equation (3)).

The continuity equation describing the balance of polymerized actin mass has both source and sink terms, whereas the total actin mass is conserved (Box 1, equation (4)). All conservation equations for scalar densities have not only convection and diffusion fluxes, but they have additional terms characteristic of activity. Indeed, both the bend and splay of a nematic director have the symmetry of a vector and, owing to the absence of time-reversal symmetry, they can enter the expression for the flux (Box 1, equation (5)). In a system with polar symmetry, there are further terms allowed by this symmetry and the absence of time-reversal invariance (Box 1, equation (6)). First, the fluxes corresponding to the same conserved quantities have a term describing a spontaneous motion with respect to the barycentric velocity along the polar direction. It provides the connection with self-propelled systems. In a close-to-equilibrium expansion, this velocity is proportional to $\Delta\mu$. Note that other terms specific to polar systems—but not associated with irreversibility—link the fluxes to hydrodynamic shear.

For the dynamics of orientational order, active terms for nematic and polar systems are different. The dynamic equation of the director field is similar to that of a passive system. In polar systems, bend and splay contribute to the dynamics of the vector field (Box 1, equation (7)). The bend contribution has the interesting property that it tends to generate Néel walls in the vector field and leads to original instabilities[16]. A feature common to all these theories is that, at long wavelengths, the systems are always unstable to inhomogeneous mobile structures, as first shown in ref. 9.

Keeping all components in the description is often cumbersome. A useful simplification is obtained by considering a one-component active system in which the hydrodynamic velocity field corresponds to the gel velocity[17]. However, caution is needed, because in the one-component description the long-wavelength limit is not consistent with the long-wavelength limit of multicomponent theories. The reason for this surprising feature is contained in a subtle multicomponent version of active gels, inspired from polymer physics and in which the stresses due to the gel are kept as an independent variable[18] (Box 1, equation (8)). This analysis shows that a one-component description is relevant only when one can neglect stresses associated with the fluid flow through the polymeric structure, characterized by a permeation constant (Box 1, equation (9)). These stresses become important at length scales larger than the screening length defined in Box 1. Educated guesses based on recent experimental results suggest that this length is of the order of 100 μm or more for the physiological actin–myosin system. A description neglecting permeation is thus often sufficient at the cell level.

As well as polar and nematic symmetries, chirality can play an interesting role in active gels. Actin filaments and microtubules have a helical structure and are chiral. As a consequence, motors not only move along filaments, but can also rotate around them[19]. Whereas in conventional nematics the difference between intrinsic rotation rate and vorticity relaxes on microscopic timescales and conservation of angular momentum is contained in conservation of linear momentum[8], it is not the case for active chiral systems. Novel active chiral terms in addition to the known passive chirality of cholesteric liquid crystals exist, which can even generate vortex-free flow in the steady state[20] (Box 1, equation (10)). Such flows can be relevant to left–right symmetry breaking in biology[21].

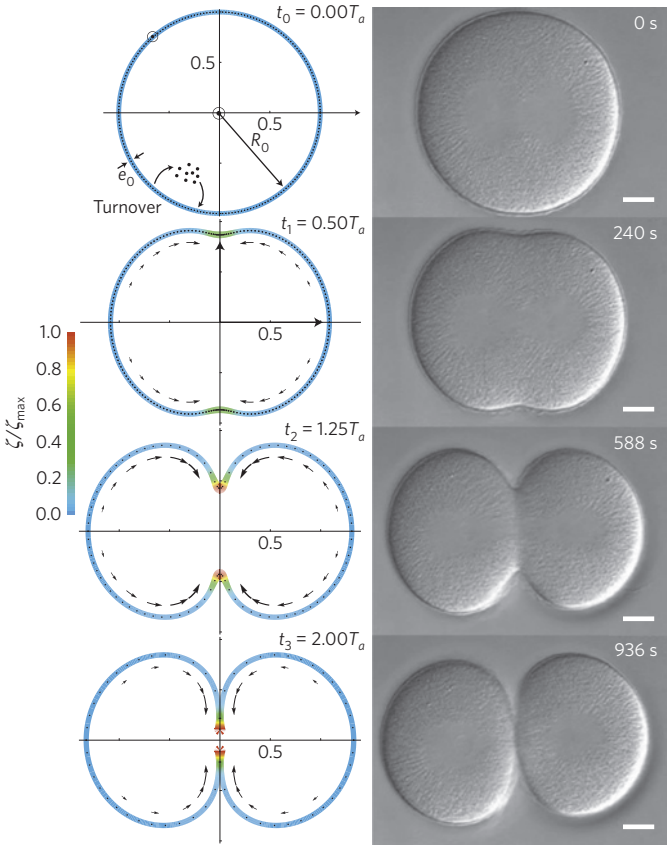

Figure 2 | The process of cytokinesis. The shape of a dividing cell, with radius R_0, at different times according to active gel theory (left) and observed for a sand dollar zygote (right). The colour code indicates active stress integrated over the thickness of the active gel. The gel thickness, e_0, is determined dynamically, taking into account filament turnover and flux balance. Arrows indicate gel flows. The characteristic time $T_a = \eta/\zeta$ is the ratio of gel viscosity and contractility. Scale bars are 20 μm. Taken from ref. 56, sand dollar figure courtesy of G. von Dassow.

The active gel picture is not limited a priori to the actin–myosin system. Any system having the same symmetries should be described by the same equations in the hydrodynamic limit. For instance, the microtubule–motor system in the long-wavelength limit should obey these equations. The real question, therefore, is whether or not under physiological conditions the long-wavelength limit is appropriate. One can also develop intermediate-length-scale theories, but this has so far mainly been done numerically[22]. At a larger scale, tissues share many common features with active gels: they behave like elastic bodies over short times and have been shown to be fluid-like over long times. Thus, the relation between stress and strain of a tissue should also contain active terms that can be either contractile or extensile.

Active gels in other domains of physics

Active gels provide an extension to soft-matter physics. Hydrodynamic theories can be extended to include, for example, active chiral systems[20] and active smectics[23]. In the case of active nematics, they can give rise to instabilities similar to the Frederiks transition of nematics[24], in which a tilted director configuration arises from a uniform director configuration on application of a sufficiently strong external field (magnetic or electric). There are two new features in active systems. First, there is no need for an external field to generate the instability and, second, the instability is characterized by the appearance of a spontaneous steady state involving motion and tilt[25], whereas in passive nematics it is characterized by the appearance of tilt only.

More general situations in two dimensions predict complex moving patterns, including excitability and defect generation[16,26–29]. Computer simulations of the equations confirm the existence of complex dynamics, reaching chaotic behaviour at large activity[28,30]. This wealth of new instabilities and low-Reynolds-number chaotic behaviour opens a new field of investigation to nonlinear physics. Furthermore, coupling the active gel theory to nonlinear chemistry—in particular, that giving rise to Turing structures—provides an important extension to the field: the domain of existence of Turing structures is vastly extended, and pattern formation occurs even for a single diffusing species[31]. In biological systems, such nonlinear chemical coupling is introduced by so-called signalling pathways.

Another domain in which active gels introduce novel physics is that of topological singularities. Rules concerning the conservation of the total topological charge are of course unchanged. The novelty arises in the way in which these singularities move. In passive systems, singularities move to minimize the free energy. In active gels, the lack of time-reversal invariance tells us that if the considered topological defect has polar symmetry, it should move, and if it has pseudo-vectorial symmetry, it should rotate—even if there is no gain in free energy. The active gel theory provides predictions for both translation[32–35] and rotation[11,12]. Charge $+1/2$ disclinations are remarkably different from $-1/2$ disclinations. The $+1/2$ disclinations have vectorial symmetry and are predicted to move, the $-1/2$ disclinations have three-fold symmetry and are predicted to be immobile. Charge $+1$ disclinations can either be immobile, or rotate[11,12]. Computer simulations have found such a behaviour in describing the self-organization of microtubules and motors[22].

Active gel theory can also impact other branches of physics, such as fracture, jamming and wetting. If the contractility is very large, the gel may rupture at short times: one then has to describe self-rupturing systems[36,37]. If the active elements are very dense, one can have active jammed states[38,39]. Active gels close to a surface on which the actin polymerization process takes place can generate a wetting layer with a very different physics from that of equilibrium wetting layers. It is controlled by contractility and polymerization rather than by temperature and pressure. In particular, its thickness is characterized by dynamical features such as polymerization/depolymerization rates[40]. This new wetting physics is relevant to the cell cortex described in the introduction. Coupling such an active layer to a fluid membrane generates equations generalizing the theory of active membranes[41].

Finally, being out-of-equilibrium structures, active gels do not obey the conventional fluctuation–dissipation theorem[42]. Low-frequency fluctuations are significantly higher than one would calculate from the response function if the system were obeying the fluctuation–dissipation theorem. This feature results from the non-equilibrium stochasticity of molecular-motor behaviour[42,43]. On the assumption of delta-correlated noise, one can predict very original diffusive behaviour for particles immersed in a gel slab. Their diffusion constant does not depend on particle size, but rather on the thickness of the slab[44]. An interesting feature concerns entangled actin solutions in the presence of motors, without passive crosslinks. The de Gennes reptation time, which for a passive polymer scales like the cube of the polymer length[45], now scales linearly owing to molecular-motor activity[46].

Biological relevance

If active gel theory can bring significant novelty in soft-condensed-matter physics does it have any relevance to biology—the very reason why it was constructed? Indeed, it may look provocative and naive to write down a set of equations intended to describe

Box 1 | Hydrodynamics of active gels.

The constitutive relation for the stress associated with an active gel in the long-time limit is

$$\sigma_{ij} = \sigma^p_{ij} + \sigma^a_{ij} \tag{1}$$

where σ_{ij} is the total stress tensor, σ^p_{ij} is that of the passive system and σ^a_{ij} is the new active part, which is

$$\sigma^a_{ij} = \zeta Q_{ij} + \bar{\zeta}\delta_{ij} \tag{2}$$

The coefficients ζ and $\bar{\zeta}$ depend on motor and filament densities, and vanish when the difference $\Delta\mu$ between the chemical potential of the fuel (in this case, ATP) and that of the reaction products vanishes. This difference drives the system out of equilibrium and thus controls the activity of the gel. The nematic order parameter in equation (2) is $Q_{ij} = \langle \pi_i\pi_j - \frac{1}{3}\delta_{ij}\rangle$, in which π_i is a unit vector in the direction of the filaments, and the average is taken over a mesoscopic volume.

The stress σ^p_{ij} is the sum of a purely hydrodynamic term $\sigma^h_{ij} = 2\eta(\partial_i v_j + \partial_j v_i - \frac{2}{3}\partial_k v_k\delta_{ij}) + \bar{\eta}\partial_k v_k\delta_{ij}$ and a term σ^{bs}_{ij}, which depends on density and the broken symmetry variables. This term is that used for equilibrium systems of the same symmetry. We ignore the tensorial nature of the viscosity η for simplicity. Here, $v_i = g_i/\rho$ is the barycentric velocity, where g_i denotes the total momentum density and ρ the total mass density. For systems sufficiently far from equilibrium, η may also depend on motor activity. There is a spontaneous tendency for the system to contract if $\bar{\zeta}$ is negative, and to expand if it is positive. Similarly, if ζ is negative (positive) the system tends to contract (expand) along the nematic or polar axis. Actin–myosin gels and muscles are known to be contractile.

Crosslinks introduce elastic behaviour on timescales shorter than their bound lifetime. Provided these times are long compared to microscopic times, introducing a 'Maxwell time', τ_M, extends the active gel description to include the elastic regime such that

$$\left(1+\tau_M\frac{D}{Dt}\right)(\sigma_{ij} - \sigma^a_{ij} - \sigma^{bs}_{ij}) = \eta\left(\partial_i v_j + \partial_j v_i - \frac{2}{3}\partial_k v_k\delta_{ij}\right) + \bar{\eta}\partial_k v_k\delta_{ij} \tag{3}$$

where we ignore the tensorial nature of τ_M for simplicity and D/Dt denotes the convected corotational time derivative. On timescales shorter than τ_M, the time derivative in equation (3) dominates, and the system behaves like an elastic medium with shear modulus η/τ_M. On timescales longer than τ_M, the time derivative can be neglected and one recovers equation (1).

The conservation equations read

$$\begin{aligned}\frac{\partial\rho_f}{\partial t} + \partial_k J^f_k &= k_p\rho_m - k_d\rho_f\\ \frac{\partial\rho_m}{\partial t} + \partial_k J^m_k &= -k_p\rho_m + k_d\rho_f\end{aligned} \tag{4}$$

where ρ_f is the mass density of monomers in the filaments, ρ_m is the mass density of free monomers, J^f_i and J^m_i are the fluxes of monomers in the filaments and free monomers respectively, and k_p and k_d are the polymerization and depolymerization rates. These rates do not obey detailed balance because the (de)polymerization process involves nucleotide hydrolysis.

For nematic systems with director n_i one can write

$$\begin{aligned}J^f_i &= J^{fp}_i + \varepsilon^f n_i\partial_k n_k + \varepsilon'^f n_k\partial_k n_i\\ J^m_i &= J^{mp}_i + \varepsilon^m n_i\partial_k n_k + \varepsilon'^m n_k\partial_k n_i\end{aligned} \tag{5}$$

The fluxes J^{fp}_i, J^{mp}_i describe convection and diffusion as in passive systems. The last two terms show that a splay and a bend of the nematic director can generate a flux. The coefficients ε^f, ε'^f, ε^m and ε'^m vanish with $\Delta\mu$.

For polar systems the lowest-order terms in a gradient expansion read

$$\begin{aligned}J^f_i &= J^{fp}_i + \lambda^f p_i + \cdots\\ J^m_i &= J^{mp}_i + \lambda^m p_i + \cdots\end{aligned} \tag{6}$$

The unit vector p_i defines the average polarization direction. The terms $v^f_i = \lambda^f p_i/\rho^f$ and $v^m_i = \lambda^m p_i/\rho^m$ are spontaneous velocities with respect to the average barycentric motion. The conservation equations for other quantities, such as motor density, can be described in a similar way.

The dynamical equations for the nematic director do not differ significantly from their passive counterpart, but the dynamical equations for the polarization do. In the long-time limit, they read

$$\begin{aligned}\frac{Dp_i}{Dt} = &-\gamma^{-1}\frac{\delta F}{\delta p_i} + \bar{\nu}p_i\partial_k v_k + \nu p_j\left(\partial_i v_j + \partial_j v_i - \frac{2}{3}\partial_k v_k\delta_{ij}\right)\\ &+ \lambda_0 p_i + \lambda_1 p_i\partial_k p_k + \lambda_2 p_k\partial_k p_i\end{aligned} \tag{7}$$

The first three terms on the right-hand side are formally identical to the expression valid for passive systems, where γ is a rotational viscosity associated with polarity changes, and ν and $\bar{\nu}$ are flow alignment coefficients describing polarity coupling to the flow field. The free energy F depends only on the gradients of the unit vector p_i, as for passive polar systems. The coefficient λ_0 can be used as a Lagrange multiplier to impose the constraint $p_k p_k = 1$. The last two terms are specific to active polar systems: the first is important in compressible systems and the second generates Néel walls and more complex instabilities, vanishing with $\Delta\mu$.

In the viscoelastic case, the filament flux contains a contribution due to the internal stress of the filament. In the long-time limit in a system with nematic order, the filament flux reads

$$J^f_i = \rho_f v_i - \gamma_f\partial_i\mu^f + \varepsilon^f n_i\partial_k n_k + \varepsilon'^f n_k\partial_k n_i + \varepsilon''^f\partial_j\sigma^f_{ij} \tag{8}$$

where $\sigma^f_{ij} = \eta^f(\partial_i v^f_j + \partial_j v^f_i - \frac{2}{3}\partial_k v^f_k\delta_{ij})$ and η^f is the viscosity of the gel. By definition, $J^f_i = \rho^f v^f_i$, so the flux equation can be written in the form of a permeation equation

$$\lambda_p(v^f_i - v_i) = -\tilde{\gamma}^f\partial_i\mu^f + \partial_j\sigma^f_{ij} + \cdots \tag{9}$$

Here, λ_p is a permeation coefficient and the ratio $(\eta^f/\lambda_p)^{1/2}$ is a screening length l. On length scales larger than l, the friction of the fluid on filaments dominates over gel stress, whereas on length scales smaller than l, the viscous stress of the filamentous structure dominates. In this latter regime, the fluid velocity relative to the gel is unimportant, and the gel velocity can be captured in a one-component description of an active gel.

For chiral systems, the constitutive relations discussed above contain many new terms. The constitutive relation for the antisymmetric part of the stress tensor in polar systems is

$$\frac{1}{2}(\sigma_{ij} - \sigma_{ji}) = \frac{1}{2}(\sigma^p_{ij} - \sigma^p_{ji}) + 2\eta'(\Omega_{ij} - \omega_{ij}) + \tilde{\zeta}\varepsilon_{ijk}p_k \tag{10}$$

where $\Omega_{ij} = \varepsilon_{ijk}\delta f/\delta l_k$ is the intrinsic rotation rate, f is the free energy density in a co-moving reference frame, l_k is the total angular momentum density and ε_{ijk} is the Levi–Civita symbol. The last term is the active term, for which $\tilde{\zeta}$ vanishes with $\Delta\mu$.

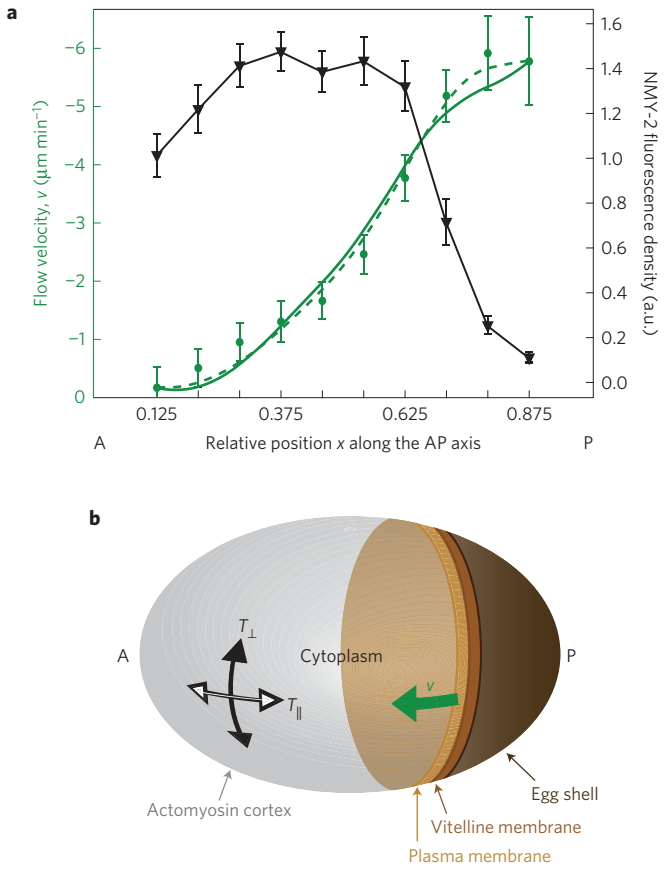

Figure 3 | Cortical flows observed in the *Caenorhabditis elegans* embryo. **a**, Measured flow velocity as a function of position along the anterior–posterior (AP) axis (green dots) shown together with the velocity calculated from active gel theory (green lines) assuming a linear relation between myosin density and contractility (solid green line) and a linear increase limited by saturation (dashed green line). The fluorescence intensity of labelled myosin motors is also shown (black triangles). **b**, Scheme of the *C. elegans* embryo, indicating the anterior and posterior sides (A and P), egg shell and underlying membranes. The anisotropy of cortical tension during flows with velocity v is indicated. $T_\parallel$, $T_\perp$ are the tensions parallel and perpendicular to the long axis of the embryo. Taken from ref. 58.

important features of biological systems simply using conservation laws and symmetries. It is well known that, in biology, details matter—and may require additional variables and more complex nonlinearities. Interestingly, the number of biological phenomena described within the simple framework of active gels is growing continuously. Among the experimental situations discussed so far are: cell motility[17,47–52], cell oscillations[53], cell division[54–57] (Fig. 2), cell wound healing[55], cortical flows[5,58] (Fig. 3), cellular hernias called 'blebs'[59], cytoplasmic and nucleus spinning[60], meiotic spindle fluctuations[61] and stress fibres[62–64]. Even plasma membrane microdomains called 'rafts' have been discussed in that context, with the suggestion that rafts co-localize with the cores of cortex disclinations[65]. Experiments on the cell cortex and lamellipodia are compatible with an active stress of the order of 0.1 to a few kPa, depending on biochemical regulation[17,59]. The associated cortical tension is more than one order of magnitude larger than the cell membrane tension[59,66]. It would be presumptuous to suggest that all features of these examples above have been captured by the simplified theory, but semi-quantitative agreement is reached. Many questions are still open, but the stage for an understanding of generic features has been set. For instance, nucleus and cytoplasmic spinning have much to do with the physics of disclinations. The longest timescale involved in cell wound healing and cell division is essentially controlled by the ratio of the active gel viscosity over contractility—both experimentally measurable quantities.

The range of applicability of active gel physics is not restricted to individual cells. One of the most fascinating applications concerns developmental biology. There is at present an impressive wealth of new experiments providing us with time series of developmental and morphogenetic processes by which complex morphologies of tissues, organs and organisms are formed[67,68]. During such processes, cells divide, rearrange and exhibit a complex collective dynamics, which on large scales can be described by generalized hydrodynamics. Even though the interacting elements are now cells rather than filaments, the same generic equations discussed for active gels apply again in this large-scale limit because the conservation laws and symmetries are similar[69–71]. In particular, cell collections can have polar or nematic symmetries[72]. Tissue dynamics is again governed over long times by active stresses and by viscoelastic material properties. Active stresses originate to a large extent from the actin–myosin system. An important model system for such dynamics is the development of the fly wing[73]. Also, processes such as zebrafish gastrulation or drosophila germ-band extension and dorsal closure have been well characterized[67]. All these processes involve active behaviour. For example, it has been suggested that the gastrulation process can be described in terms of active gel theory[74]. Clearly the understanding of many other developmental processes will involve the use of active gel theory, coupled to biochemical signalling.

In vitro experiments

Biological systems are often restricted to the narrow working conditions set by evolution[75]. However, it is always useful to vary parameters in large ranges—hence the need for simple and well-controlled *in vitro* experiments. Early *in vitro* experiments with cell extracts[76,77] confirmed the spontaneous contractility of the acto-myosin system, but cell extracts have too many components to allow access to simple quantitative information. More recent experiments[78] have confirmed and sharpened earlier results[79], showing that gels contract significantly, not only if they contain a minimum motor concentration, but also if they contain a concentration of passive linkers set in a well-defined range.

As stated in the introductory remarks, most of the cell mechanical activity is due to the cortex, a thin layer of actin–myosin gel. Naturally, experimentalists tried to reconstitute such a layer. This is a difficult task, because one not only has to mimic the active gel, but also the cell plasma membrane. This has been achieved by using giant phospholipidic vesicles loaded by actin and nucleators. Early experiments omitted myosin motors[80]. Experiments including motors were subsequently performed, but with the artificial cortex on the exterior of the vesicle rather than on the interior[81] or on a supported bilayer[82]. This system showed contractility and symmetry breaking, but extracting full quantitative data proved difficult.

A simpler system that retains the feature of having an interface separating an interior and an exterior is that of a water droplet, immersed in oil and containing all necessary constituents[83]. Provided that the nucleators bind preferentially at the oil–water interface, one can obtain a layer similar to the cortex. This permits one to quantitatively investigate the conditions necessary for obtaining contractility. A symmetry-breaking transition from a uniform gel layer to a gel thickness distribution around the droplet with polar symmetry can be observed, provided that contractility is large enough. This observation is in qualitative agreement with theoretical expectations[53]. Finally, collections of actin filaments interacting with myosin motors near a glass surface show a beautiful complex phase space with moving structures, characteristic of self-propelling objects[84,85].

Active gels need not be based on the actin–myosin interaction alone. There are a priori many other ways to make such gels. The second natural choice is the microtubule–kinesin system. This was used early on to show that one could generate *in vitro* self-organized structures[22] by mixing tetrameric kinesins and microtubules in the presence of ATP. Using the language of physics, these experiments showed that, with suitable boundary conditions, the microtubule–kinesin system could generate $+1$ disclinations. They could, in appropriate regions of phase space, give rise to rotating patterns. Both simulations[22] and analytical solutions of active gel equations[11,12] agree with these findings. More recently, an interesting feature has been added: a tunable attractive interaction between microtubules has been introduced by using the depletion interaction generated by a solution of polyethylene glycol (PEG; ref. 86). In this case, one obtains, in appropriate regions of phase space, active extensile anisotropic systems. They exhibit spontaneous motion and the generation of $\pm 1/2$ disclinations, which indicates an active nematic. As expected on symmetry grounds, $+1/2$ disclinations exhibit spontaneous active motion, whereas $-1/2$ disclinations do not[32–35]. A very interesting geometry is obtained by embedding droplets of this microtubule–kinesin–PEG system in oil. The microtubules spontaneously segregate at the oil–water interface, owing to a depletion interaction, and for small enough droplets one obtains an active two-dimensional nematic on a sphere. As expected with passive nematics, such spheres should be decorated by four $+1/2$ disclinations located at the vertices of a tetrahedron. The interesting observation is that for moderate activity the disclinations oscillate between two possible configurations of the tetrahedron, whereas for larger activity the vesicle shape is strongly modified[33]. The oscillating regime can be described analytically, whereas both the periodic and the chaotic regimes are found using numerical solutions of the active nematic equations[33].

A new and clever way of creating active nematics has recently been invented by mixing bacteria and non-toxic lyotropic liquid crystals[87,88]. Concentrations of bacteria as low as 0.2% volume fraction can create large-scale spontaneous motion and structures characteristic of active nematics. At large activity, controlled by the bacterium concentration and oxygen content of the solution, a chaotic regime of spontaneously generated disclinations is reached, as also seen in the microtubule system. This new class of active matter opens the possibility for investigating other liquid crystalline phases, such as active cholesterics.

Challenges

By writing down generic equations in the hydrodynamic limit, one has replaced a hundred thousand variables by only a few in a field theory. From our experience in soft condensed matter, one can infer that the space of solutions is still large enough to describe most experimental situations within a unified framework. The dependence on microscopic details is not suppressed, but it comes through complex state diagrams depending on the effective parameters of the theory. These parameters depend themselves on molecular details. They can be measured experimentally and calculated from microscopic theories or by simulations. Some aspects of biological systems do escape this generic description. The active gel theory has to be complemented by what is commonly called signalling. Note that signalling pathways can depend in subtle ways on mechanical stresses[89], which brings a further twist to the nonlinear physics aspect of active gel behaviour.

One could write a long list of problems that remain open at the cell level. But the tools are there, and we may reasonably hope to obtain a coherent picture of cell dynamics, including the nucleus. Another important question concerns how this new physics translates to higher levels of organization in a developing individual—giving rise to tissues and organs. We think active gel theory will be an important tool for developing a quantitative understanding of developmental biology. Last, a great deal remains to be done in the study of fluctuations in active gels, in cells and in tissues. It raises the very interesting question of the generalization of fluctuation theorems to living organisms.

Received 24 September 2014; accepted 10 December 2014; published online 3 February 2015

References

1. Alberts, B. *et al. Molecular Biology of the Cell* 5th edn (Garland Science, 2008).
2. Janmey, P. A., Euteneuer, U., Traub, P. & Schliwa, M. Viscoelastic properties of vimentin compared with other filamentous biopolymer networks. *J. Cell. Biol.* **113,** 155–160 (1991).
3. Herrmann, H., Bär, H., Kreplak, L., Strelkov, S. V. & Aebi, U. Intermediate filaments: from cell architecture to nanomechanics. *Nature Rev. Mol. Cell. Biol.* **8,** 562–573 (2007).
4. Bausch, A. R. & Kroy, K. A bottom up approach to cell mechanics. *Nature Phys.* **2,** 231–236 (2006).
5. Salbreux, G., Charras, G. & Paluch, E. Actin cortex mechanics and cellular morphogenesis. *Trends Cell Biol.* **3722,** 536–545 (2012).
6. Marchetti, M. C. *et al.* Hydrodynamics of soft active matter. *Rev. Mod. Phys.* **85,** 1143–1189 (2013).
7. Steinberg, I. Z., Oplatky, A. & Katchalsky, A. Mechanochemical engines. *Nature* **201,** 568–571 (1966).
8. Martin, P. C., Parodi, O. & Pershan, P. S. Unified hydrodynamic theory for crystals, liquid crystals and normal fluids. *Phys. Rev. A* **6,** 2401–2420 (1972).
9. Simha, R. A. & Ramaswamy, S. Hydrodynamic fluctuations and instabilities in ordered suspensions of self-propelled particles. *Phys. Rev. Lett.* **89,** 058101 (2002).
10. Hatwalne, Y., Ramaswamy, S., Rao, M. & Simha, R. A. Rheology of active-particle suspensions. *Phys. Rev. Lett.* **92,** 118101 (2004).
11. Kruse, K., Joanny, J-F., Jülicher, J., Prost, J. & Sekimoto, K. Asters, vortices, and rotating spirals in active gels of polar filaments. *Phys. Rev. Lett.* **92,** 078101 (2004).
12. Kruse, K., Joanny, J-F., Jülicher, J., Prost, J. & Sekimoto, K. Generic theory of active polar gels: A paradigm for cytoskeletal dynamics. *Eur. Phys. J. E* **16,** 5–16 (2005).
13. Kruse, K. & Jülicher, J. Actively contracting bundles of polar filaments. *Phys. Rev. Lett.* **85,** 1778–1781 (2000).
14. Liverpool, T. B. & Marchetti, M. C. Instabilities of isotropic solutions of active polar filaments. *Phys. Rev. Lett.* **90,** 138102 (2003).
15. Liverpool, T. B. & Marchetti, M. C. Bridging the microscopic and the hydrodynamic in active filament solutions. *Europhys. Lett.* **69,** 846–852 (2005).
16. Giomi, L., Marchetti, M. C. & Liverpool, T. Complex spontaneous flows and concentration banding in active polar films. *Phys. Rev. Lett.* **101,** 198101 (2008).
17. Kruse, K., Joanny, J. F., Jülicher, F. & Prost, J. Contractility and retrograde flow in lamellipodium motion. *Phys. Biol.* **3,** 130–137 (2006).
18. Callan-Jones, A. C. & Jülicher, F. Hydrodynamics of active permeating gels. *New J. Phys.* **13,** 093027 (2011).
19. Sase, I., Miyata, H., Ishiwata, S. & Kinosita, K. Jr Axial rotation of sliding actin filaments revealed by single-fluorophore imaging. *Proc. Natl Acad. Sci. USA* **94,** 5646–5650 (1997).
20. Fürthauer, S., Strempel, M., Grill, S. W. & Jülicher, F. Active chiral fluids. *Eur. Phys. J. E* **35,** 89 (2012).
21. Fürthauer, S., Strempel, M., Grill, S. W. & Jülicher, F. Active chiral processes in thin films. *Phys. Rev. Lett.* **110,** 048103 (2012).
22. Nedelec, F., Surrey, T., Maggs, A. C. & Leibler, S. Selforganization of microtubules and motors. *Nature* **389,** 305–308 (1997).
23. Adhyapak, T. C., Ramaswamy, S. & Toner, J. Live soap: stability, order, and fluctuations in apolar active smectics. *Phys. Rev. Lett.* **110,** 118102 (2013).
24. De Gennes, P. G. & Prost, J. *The Physics of Liquid Crystals* (Clarendon Press, 1993).
25. Voituriez, R., Joanny, J. F. & Prost, J. Spontaneous flow transition in active polar gels. *Europhys. Lett.* **70,** 404–410 (2005).
26. Voituriez, R., Joanny, J. F. & Prost, J. Generic phase diagram of active polar films. *Phys. Rev. Lett.* **96,** 28102 (2006).
27. Giomi, L., Mahadevan, L., Chakraborty, B. & Hagan, M. F. Excitable patterns in active nematics. *Phys. Rev. Lett.* **106,** 218101 (2011).
28. Giomi, L., Mahadevan, L., Chakraborty, B. & Hagan, M. F. Banding, excitability and chaos in active nematic suspensions. *Nonlinearity* **25,** 2245–2269 (2012).
29. Ramaswamy, S. & Rao, M. Active-filament hydrodynamics: instabilities, boundary conditions and rheology. *New J. Phys.* **9,** 423 (2007).

30. Fielding, S. M., Marenduzzo, D. & Cates, M. E. Nonlinear dynamics and rheology of active fluids: Simulations in two dimensions. *Phys. Rev. E* **83,** 041910 (2011).
31. Bois, J. S., Jülicher, F. & Grill, S. W. Pattern formation in active fluids. *Phys. Rev. Lett.* **106,** 028103 (2011).
32. Giomi, L., Bowick, M. J., Ma, X. & Marchetti, M. C. Defect annihilation and proliferation in active nematics. *Phys. Rev. Lett.* **110,** 228101 (2013).
33. Keber, F. C. *et al.* Topology and dynamics of active nematic vesicles. *Science* **345,** 1135–1139 (2014).
34. Thampi, S. P., Golestanian, R. & Yeomans, J. M. Velocity correlations in an active nematic. *Phys. Rev. Lett.* **111,** 118101 (2013).
35. Pismen, L. M. Dynamics of defects in an active nematic layer. *Phys. Rev. E* **88,** 050502 (2013).
36. Wang, H. *et al.* Necking and failure of constrained 3D microtissues induced by cellular tension. *Proc. Natl Acad. Sci. USA* **110,** 20923–20928 (2013).
37. Sheinman, M., Sharma, A., Alvarado, J., Koenderink, G. H. & MacKintosh, F. C. Active biopolymer networks generate scale-free but Euclidean clusters. Preprint at http://arxiv.org/abs/1402.2623 (2014).
38. Berthier, L. & Kurchan, J. Non-equilibrium glass transitions in driven and active matter. *Nature Phys.* **9,** 310314 (2013).
39. Henkes, S., Fily, Y. & Marchetti, M. C. Active jamming: Self-propelled soft particles at high density. *Phys. Rev. E* **84,** 040301 (2011).
40. Joanny, J-F., Kruse, K., Prost, J. & Ramaswamy, S. The actin cortex as an active wetting layer. *Eur. Phys. J. E* **36,** 52 (2013).
41. Maitra, A., Srivastava, P., Rao, M. & Ramaswamy, S. Activating membranes. *Phys. Rev. Lett.* **112,** 258101 (2014).
42. Mizuno, D., Tardin, C., Schmidt, C. F. & MacKintosh, F. C. Nonequilibrium mechanics of active cytoskeletal networks. *Science* **315,** 370–373 (2007).
43. Levine, A. J. & MacKintosh, F. C. The mechanics and fluctuation spectrum of active gels. *J. Phys. Chem. B* **113,** 3820–3830 (2009) (P-G. de Gennes memorial issue).
44. Basu, A., Joanny, J-F., Jülicher, F. & Prost, J. Anomalous behavior of the diffusion coefficient in thin active films. *New. J. Phys.* **14,** 115001 (2012).
45. De Gennes, P. G. *Scaling Concepts in Polymer Physics* (Cornell Univ. Press, 1979).
46. Humphrey, D., Duggan, C., Saha, D., Smith, D. & Käs, J. Active fluidization of polymer networks through molecular motors. *Nature* **416,** 413–416 (2002).
47. Callan-Jones, A., Joanny, J. F. & Prost, J. Viscous-fingering-like instability of cell fragments. *Phys. Rev. Lett.* **100,** 258106 (2008).
48. Callan-Jones, A. & Voituriez, R. Active gel model of amoeboid cell motility. *New. J. Phys.* **15,** 025022 (2013).
49. Tjhung, E., Marenduzzo, M. & Cates, M. E. Spontaneous symmetry breaking in active droplets provides a generic route to motility. *Proc. Natl Acad. Sci. USA* **109,** 12381–12386 (2012).
50. Shao, D., Rappel, W. J. & Levine, H. Computational model for cell morphodynamics. *Phys. Rev. Lett.* **105,** 108104 (2010).
51. Hawkins, R. W. *et al.* Spontaneous contractility-mediated cortical flow generates cell migration in three-dimensional environments. *Biophys. J.* **101,** 1041–1045 (2011).
52. Blanch-Mercader, C. & Casademunt, J. Spontaneous motility of actin lamellar fragments. *Phys. Rev. Lett.* **110,** 078102 (2013).
53. Salbreux, G., Joanny, J. F., Prost, J. & Pullarkat, P. Shape oscillations of non-adhering fibroblast cells. *Phys. Biol.* **4,** 268–284 (2007).
54. He, X. & Dembo, M. On the mechanics of the first cleavage division of the sea urchin egg. *Exp. Cell Res.* **233,** 252–273 (1997).
55. Salbreux, G., Prost, J. & Joanny, J-F. Hydrodynamics of cellular cortical flows and the formation of contractile rings. *Phys. Rev. Lett.* **103,** 058102 (2009).
56. Turlier, H., Audoly, B., Prost, J. & Joanny, J. F. Furrow constriction in animal cell cytokinesis. *Biophys. J.* **106,** 114–123 (2014).
57. Sedzinski, J. *et al.* Polar actomyosin contractility destabilizes the position of the cytokinetic furrow. *Nature* **476,** 462–466 (2011).
58. Mayer, M., Depken, M., Bois, J. S., Jülicher, F. & Grill, S. W. Anisotropies in cortical tension reveal the physical basis of polarizing cortical flows. *Nature* **467,** 617–621 (2010).
59. Tinevez, J. Y. *et al.* Role of cortical tension in bleb growth. *Proc. Natl Acad. Sci. USA* **106,** 18581–18586 (2009).
60. Kumar, A., Maitra, A., Sumit, M., Ramaswamy, S. & Shivashankar, G. V. Actomyosin contractility rotates the cell nucleus. *Sci. Rep.* **4,** 3781 (2013).
61. Brugues, J. & Needleman, D. J. Physical basis of spindle self-organisation. *Proc. Natl Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1409404111 (2014).
62. Nicolas, A., Besser, A. & Safran, S. A. Is the mechanics of cell-matrix adhesion amenable to physical modeling? *J. Adhes. Sci. Technol.* **24,** 2203–2214 (2010).
63. Schwarz, U. S., Erdmann, T. & Bischofs, I. B. Focal adhesions as mechanosensors: The two-spring model. *Biosystems* **83,** 225–232 (2006).
64. Marcq, P., Yoshinaga, N. & Prost, J. Rigidity sensing explained by active matter theory. *Biophys. J.* **101,** L33–L35 (2011).
65. Goswami, D. *et al.* Nanoclusters of GPI-anchored proteins are formed by cortical actin-driven activity. *Cell* **135,** 1085–1097 (2008).
66. Fischer-Friedrich, E., Hyman, A. A., Jülicher, F., Müller, D. & Helenius, J. Quantification of surface tension and internal pressure generated by single mitotic cells. *Sci. Rep.* **4,** 6213 (2014).
67. Lecuit, T. & Lenne, P-F. Cell surface mechanics and the control of cell shape, tissue patterns and morphogenesis. *Nature Rev. Mol. Cell Biol.* **102,** 633–644 (2007).
68. Heisenberg, C. P. & Bellaïche, Y. Forces in tissue morphogenesis and patterning. *Cell* **153,** 948–962 (2013).
69. Bittig, T., Wartlick, O., Kicheva, A., Gonzalez-Gaitan, M. & Jülicher, F. Dynamics of anisotropic tissue growth. *New J. Phys.* **10,** 063001 (2008).
70. Ranft, J. *et al.* Fluidization of tissues by cell division and apoptosis. *Proc. Natl Acad. Sci. USA* **107,** 20863–20868 (2010).
71. Delarue, M., Joanny, J. F., Jülicher, F. & Prost, J. Stress distributions and cell flows in a growing cell aggregate. *Interface Focus* **4,** 20140033 (2014).
72. Gruler, H. Fluid self-organized machines. *Liquid Crystals* **24,** 49–66 (1998).
73. Aigouy, B. *et al.* Cell flow reorients the axis of planar polarity in the wing epithelium of Drosophila. *Cell* **142,** 773–786 (2010).
74. Behrndt, M. *et al.* Forces driving epithelial spreading in zebrafish gastrulation. *Science* **338,** 257–260 (2012).
75. Sheftel, H., Shoval, O., Mayo, A. & Alon, U. The geometry of the Pareto front in biological phenotype space. *Ecol. Evol.* **3,** 1471–1483 (2013).
76. Loewy, A. G. An actomyosin-like substance from the plasmodium of a myxomycete. *J. Cell. Comp. Physiol.* **40,** 127–156 (1952).
77. Bettex-Galland, M. & Lüscher, E. F. Extraction of an actomyosin-like protein from human thrombocytes. *Nature* **185,** 276–277 (1959).
78. Bendix, P. M. *et al.* A quantitative analysis of contractility in active cytoskeletal protein networks. *Biophys. J.* **94,** 3126–3136 (2008).
79. Ebashi, S., Ebashi, F. & Maruyama, K. A new protein factor promoting contraction of actomyosin. *Nature* **203,** 645–646 (1964).
80. Sengupta, K. *et al.* Coupling artificial actin cortices to biofunctionalized lipid monolayers. *Langmuir* **22,** 5776–5785 (2006).
81. Carvalho, K. *et al.* Cell-sized liposomes reveal how actomyosin cortical tension drives shape change. *Proc. Natl Acad. Sci. USA* **110,** 16456–16461 (2013).
82. Murrell, M. & Gardel, M. L. Actomyosin sliding is attenuated in contractile biomimetic cortices. *Mol. Biol. Cell* **25,** 1845–1853 (2014).
83. Shah, E. A. & Keren, K. Symmetry breaking in reconstituted actin cortices. *eLife* **3,** e01433 (2014).
84. Köhler, S., Schaller, V. & Bausch, A. R. Structure formation in active networks. *Nature Mater.* **10,** 462–468 (2011).
85. Gordon, D., Bernheim-Groswasser, A., Kaesar, C. & Farago, O. Hierarchical self-organization of cytoskeletal active networks. *Phys. Biol.* **9,** 026005 (2012).
86. Sanchez, T., Chen, D. T. N., DeCamp, S. J., Heymann, M. & Dogic, Z. Spontaneous motion in hierarchically assembled active matter. *Nature* **491,** 431–434 (2012).
87. Mushenheim, Peter C. *et al.* Dynamic self-assembly of motile bacteria in liquid crystals. *Soft. Matter* **10,** 88–95 (2014).
88. Shuang, Z., Sokolov, A., Lavrentovich, O. D. & Aranson, I. S. Living liquid crystals. *Proc. Natl Acad. Sci. USA* **111,** 1265–1270 (2014).
89. Iskratsch, T., Wolfenson, H. & Sheetz, M. P. Appreciating force and shape—the rise of mechanotransduction in cell biology. *Nature Rev. Mol. Cell Biol.* **15,** 825–833 (2014).

Acknowledgements

We thank S. Grill, K. Kruse, C. Marchetti and S. Ramaswamy for many interesting discussions, and S. Marbach and H. Turlier for providing Figs 1 and 2.

Additional information

Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to F.J.

Competing financial interests

The authors declare no competing financial interests.