Active gels as a description of the actin-myosin cytoskeleton

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This short review presents a qualitative introduction to the hydrodynamic theory of active polar gels and its applications to the mechanics of the cytoskeleton. Active polar gels are viscoelastic materials formed by polar filaments maintained in a nonequilibrium state by constant consumption of energy. In the cytoskeleton of eukaryotic cells, actin filaments are treadmilling and form a viscoelastic gel interacting with myosin molecular motors driven by the hydrolysis of adenosine triphosphate; one can thus consider the actomyosin cytoskeleton as an active polar gel. The hydrodynamic description is generic as it only relies on symmetry arguments. We first use the hydrodynamic approach to discuss the spontaneous generation of flow in an active polar film. Then we give two examples of applications to lamellipodium motility and to instabilities of cortical actin.
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Most cellular processes critically depend on the mechanical properties of the cytoskeleton (Alberts *et al.*, 2002). When a cell enters mitosis, for example, the contractility of the actin cytoskeleton increases, and the cell becomes roughly spherical. In many cells, actin forms a cortical layer just below the plasma membrane where it interacts with myosin molecular motors. The motors create internal stresses in the cortical layer. During mitosis, the increased activity of the myosin motors drives an increase of the cortical layer tension. The cytoskeleton also plays a crucial role in the later stages of cell division where the assembly of an actin ring under tension initiates the formation of the cleavage furrow that eventually leads to the separation of the two daughter cells.

Cell adhesion and cell motility are also strongly cytoskeleton dependent (Bershadsky *et al.*, 2006; Verkhovsky *et al.*, 2003). The adhesion proteins of a cell on a substrate or with another cell are connected to the actin cytoskeleton,

and the adhesion strength is clearly related to the mechanical properties and the contractility of the cytoskeleton. Cell motility on a solid substrate is traditionally decomposed into three steps, protrusion associated with actin polymerization at the leading edge, adhesion by formation of focal contacts, and retraction at the back of the cell. All these steps again depend on the mechanical properties of the actin cytoskeleton (Alberts *et al.*, 2002).

These examples clearly show that a quantitative description of the mechanical properties and the contractility of the cytoskeleton are needed to describe most cellular processes. Electron micrographs show strongly entangled actin filaments in the cytoskeleton (Verkhovsky *et al.*, 2003), and many proteins are known to act as cross-links between actin filaments (Bray, 2001). From a polymer physics point of view, the actin cytoskeleton can therefore be considered as a polymer gel (DeGennes, 1981). The gel can have either temporary cross-links (physical

gel) or permanent cross-links (chemical gel) depending on the lifetime of the association between the cross-linking proteins and actin as compared to the experimental time. The mechanical response at short time scales after a perturbation is an elastic response characterized by a finite elastic shear modulus E . The actin gel is a very soft material, and its elastic modulus is in the range of 10^3 – 10^4 Pa (Wottawah *et al.*, 2005). At longer time scales, actin flows and has a finite viscosity η . In *in vitro* experiments on actin, the characteristic viscoelastic relaxation time τ where actin starts to flow is on the order of 100–1000 s (Wottawah *et al.*, 2005). In the simplest viscoelastic model proposed by Maxwell (Larson, 1988), the viscosity is related to the elastic modulus and the viscoelastic relaxation time by the so-called Maxwell relation $\eta = E\tau$. In the absence of molecular motors [or if there is no motor activity, in the absence of adenosine triphosphate (ATP)], the mechanical properties of the actin gel can be studied using the well-established methods of polymer physics. This passive description though does not provide a realistic description of the cytoskeleton because it ignores the interactions between actin and myosin molecular motors.

Myosin II are nonprocessive motor proteins, which bind onto actin filaments and undergo a conformational change called the power stroke upon ATP hydrolysis (Howard, 2001). In the cytoskeleton, myosin motors do not act individually but form aggregates known as minifilaments (Verkhovsky *et al.*, 1999). The minifilaments by binding to the actin filaments somehow act as “disordered micro-muscles,” they create internal stresses that contract the actin meshwork. The interaction between the actin network and molecular motors completely changes the nature of the physical properties of the cytoskeleton: the cytoskeleton is fueled by ATP and constantly consumes energy; it is therefore out of equilibrium, and the classical description of a gel at thermodynamic equilibrium cannot be used. Myosins are not the only source of ATP consumption in the cytoskeleton, actin treadmilling is also a nonequilibrium process, which as well requires the consumption of ATP (Medeiros *et al.*, 2006). We refer here to a system maintained out of equilibrium by energy consumption as an active system and to the cytoskeleton as an active gel (Julicher *et al.*, 2007).

The study of an active system such as the cytoskeleton cannot rely on a thermodynamic approach based on a free energy minimization; it must thus rely on a dynamic theory reflecting the local force balance in the system. This can be done in two ways. One can first write microscopic equations for actin filaments interacting with molecular motors and then coarse-grain these equations to a mesoscopic or a macroscopic scale to obtain the mechanical properties of the cytoskeleton at large length scales (Kruse and Julicher, 2000; Liverpool and Marchetti, 2005; Aranson and Tsimring, 2005). In this approach, one needs, however, a refined microscopic description of both the properties of actin filaments and the properties of molecular motors. An alterna-

tive approach which has proved useful, for example, to study the physics of liquid crystals, is to consider only the system over large length scales and long time scales and build up what is called a hydrodynamic theory. The properties of the system are then described by a small set of macroscopic variables (conserved quantities, order parameters) and phenomenological relations between these variables are written (the constitutive equations) with the only constraint that they must respect the symmetries of the problem. We use this approach here and build up a hydrodynamic theory of active gels (Julicher *et al.*, 2007; Simha and Ramaswamy, 2002). The microscopic and the macroscopic descriptions are not incompatible: the coarse-graining of the microscopic equations must lead to macroscopic equations, which respect the symmetries of the hydrodynamic theory. In addition, the microscopic approach provides explicit expressions of the phenomenological constants introduced in the hydrodynamic theory as a function of the microscopic properties of actin and myosins. These expressions, however, depend on the model used at the microscopic scale. The hydrodynamic theory itself is generic and does not depend on any microscopic model, in the sense that it is only based on symmetries and not on any detailed microscopic description of the various components and their interactions. The hydrodynamics of any simple liquid is, for example, characterized by a single parameter the viscosity (Landau and Lifschitz, 2000). A microscopic kinetic theory is needed, however, to calculate the viscosity of each liquid as a function of its molecular properties. Alternatively, the parameters introduced in a hydrodynamic theory can be measured experimentally. For the cytoskeleton, the parameters which define the mesoscopic behavior are the same as those of liquid crystals at long time scales (DeGennes and Prost, 1993) and as that of gels at short time scales (DeGennes, 1981) with the only addition of terms describing the contractility. All these parameters are therefore, in principle, accessible using known experimental techniques.

Several theoretical descriptions of cell motility and of the cytoskeleton focus on the kinetics of actin polymerization at the leading edge of an advancing cell. The advancing velocity of the cell is then related to the various parameters associated with actin polymerization such as the rates of nucleation, capping or polymerization, or the membrane resistance (Dawes *et al.*, 2006; Mogilner and Edelstein-Keshet, 2002). A recent application of these ideas to motile keractocyte cells is given in Lacayo *et al.* (2007). A general review of the mechanical properties of the cytoskeleton of adherent cells is given in Stamenovic and Ingber (2002). A last way to study the cytoskeleton quantitatively is to use numerical simulations (Marenduzzo *et al.*, 2007). This has been done in detail in cases where the cytoskeleton has few constituents, for example, to study the role of microtubules in yeast cells or in *C. elegans* embryos (Janson *et al.*, 2007; Kozlowski *et al.*, 2007).

This short review is organized as follows. In the “Actin Filaments and Myosin Motors: Mesoscopic Descriptions of the Cytoskeleton” section, we give a short account of the microscopic theories of the cytoskeleton. In the “Active Gel Theory of the Cytoskeleton” section, we introduce qualitatively the hydrodynamic theory of active gels. We then illustrate this theory by discussing the flow properties of active gels in the “Spontaneous Flow and Instabilities of Active Gels” section, and some applications to properties of cells, such as lamellipodium motion and cortical actin in the “Active Gel Description of Cellular Properties: Lamellipodium Motion, Cortical Actin” section. The “Discussion” section expresses both limitations and further improvements of the theory together with its relevance to a variety of biological systems. We stress in particular its potential use for the description of tissue dynamics.

ACTIN FILAMENTS AND MYOSIN MOTORS: MESOSCOPIC DESCRIPTIONS OF THE CYTOSKELETON

A spectacular *in vitro* experiment has been recently performed in the group of Schmidt, which directly shows the role of the activity of molecular motors in the cytoskeleton (Mizuno *et al.*, 2007). Actin filaments in this experiment are permanently cross-linked and form an elastic gel with a finite elastic shear modulus (Storm *et al.*, 2005). Myosin II motors are added to this actin gel, and the rheology of the actomyosin complex is measured by the so-called micro-rheology approach studying the motion of small colloidal spheres in the gel. In the absence of ATP, the motors are not active, and the position fluctuations of the bead are hardly observable in an optical microscope. The system behaves as a classical thermal equilibrium system. In an equilibrium system, one can measure independently the time power spectrum of the fluctuation of any variable such as the bead position in this experiment and the response of this variable to an external perturbation, which is periodic in time. The imaginary part of this response (i.e., the component of the response, which has a phase $\pi/2$ with respect to the perturbation) is associated with the dissipation in the system. The so-called fluctuation-dissipation theorem (Chandler, 1987) states that the power spectrum of the fluctuations and the imaginary part of the response function are proportional and that the proportionality constant does not depend on frequency but only on the equilibrium temperature. One can perform independent measurements of the autocorrelation function of the bead positions and of the linear response function of the bead positions to an external oscillatory force. As stated by the fluctuation-dissipation theorem, a suitable ratio of the correlation function over the response function provides a measure of the temperature at which the experiment is performed.

On the contrary, in the presence of ATP the bead positions show much higher fluctuations, which are directly ob-

servable under the microscope. These fluctuations are directly related to the stress fluctuations in the gel due to the molecular motors. In this case, the fluctuation dissipation theorem is not satisfied, and no proper equilibrium temperature can be defined for this system.

This experiment is almost quantitatively described by the authors using a microscopic theory for actin filaments and myosin molecular motors. Actin filaments can be described as classical semiflexible polymers. Their mechanical properties are characterized by a single parameter, the persistence length l_p (DeGennes, 1981). This is the length beyond which an actin filament can no longer be considered as a rigid rod because of thermal fluctuations and over which a filament loses the memory of its orientation. The persistence length of an actin filament is on the order of $l_p = 10 \mu\text{m}$ and in a cell actin filament cannot be considered as rigid rods; they show bending fluctuations (Isambert *et al.*, 1995). When a stretching force is applied to an actin filament of length L , the actin filament responds as a spring with a spring constant $\kappa \sim kTl_p^2/L^4$, where T is temperature and k is the Boltzmann constant (MacKintosh *et al.*, 1995). The elastic modulus of the actin gel can be estimated by considering a network of connected springs and scales as $E \approx kTl_p^2/L^5$. Using for L the typical mesh size of an actin gel ($L \sim 150 \text{ nm}$) we obtain a very small elastic modulus on the order of $10^3 - 10^4 \text{ Pa}$ (MacKintosh *et al.*, 1995). When a tension σ is applied to an actin filament the filament stiffens and its spring constant k increases strongly with the applied tension as $\sigma^{3/2}$. Such stiffening of the filaments is directly observed in the experiments of Mizuno *et al.* (2007) and is interpreted as the stiffening due to the forces exerted by myosin motors on the actin filaments.

Myosin motors are proteins composed of a tail and two heads that tend to bind on actin filaments and walk toward the barbed end of the actin filaments (Howard, 2001). A single motor is, however, nonprocessive and detaches from the filament after one step giving, therefore, only a kick to the filament. In the cytoskeleton, the myosin molecules bind together to form clusters of several motors (of order 20), which are often called minifilaments. A myosin cluster is more processive. In the absence of any force, a myosin cluster walks along the actin filaments always toward the barbed end of the filament at a finite velocity v_m on the order of a micrometer per second. When a force is applied to the cluster opposing the motion, the velocity decreases and eventually vanishes at the so-called stall force f_s , which is on the order of a few piconewtons. Several molecular or mesoscopic models have been built to describe the motion of motor clusters on filaments; we refer to Julicher *et al.* (1997) for a review.

In the cytoskeleton or in an *in vitro* actin-myosin gel, the motor clusters (or minifilaments) create effective cross-links between the filaments, and their activity induces internal stresses by pulling on the filaments. In the case where the

actin filaments are not cross-linked, at long time scales the system has a liquidlike behavior. The active internal stress has been calculated by Kruse and Julicher (2000) in the simplified case of fully parallel filament collections. The active stress is then due to filaments with the same polarity bound by a motor dimer (each motor in the dimer walking on one filament). The motor dimer advances at a velocity v_m until it reaches the end of one filament. The contractile stress is then due to the fact that the motor does not unbind instantaneously from the filament end. The obtained contractile stress is $\sigma_{\text{act}} \sim -c_m \eta v_m^2 \tau_i L$ where c_m is the motor density, η is the viscosity, L is the length of the filaments, and τ_i is the unbinding time from the filament end points. An order of magnitude estimate of the stress in a three-dimensional gel is obtained by replacing L by the mesh size of the gel. A more detailed study of this liquid limit has been performed in a series of papers by Liverpool and Marchetti (Liverpool and Marchetti, 2005) in the limit where the actin concentration is very low.

In the opposite limit actin has permanent cross-links, the motor clusters pull on two filaments and exert a force dipole of the two filaments with a force on each filament on the order of the stall force f_m . A naive scaling description would then lead to a contractile stress on the order of $\sigma_{\text{act}} \sim -p c_m f_m L$, where p is the probability that a motor cluster is bound to two filaments. Taking $c_m = 1/L^3$, $L = 100$ nm, and $p = 1/10$, this gives a contractile stress on the order of 1000 Pa. A refined description of this limit is given in Nadrowski *et al.* (2004).

ACTIVE GEL THEORY OF THE CYTOSKELETON

We now describe the opposite strategy and consider the cytoskeleton at large length scales compared to the mesh size of the gel and long time scales compared to the typical conformational relaxation times of the actin filaments, to build up a hydrodynamic theory. The macroscopic variables that must then be considered are dictated by the symmetries of the problem and the conservation laws. For a simple isotropic liquid, the variables that must be considered are the stress σ and the velocity gradient u given by the spatial derivatives of the velocity v . These are tensorial quantities but, in order to keep the discussion at a simple qualitative level, we ignore here the tensorial indices. For a simple liquid such as water, the stress is proportional to the velocity gradient $\sigma = 2\eta u$, where η is the macroscopic viscosity and u is the velocity gradient. The equations of motion of a simple fluid are obtained by combining this constitutive equation with the force balance equation leading to the Stokes or the Navier–Stokes equation (Landau and Lifschitz, 2000).

In the case where the liquid molecules are not isotropic but polar, the liquid itself can be polar meaning that the molecules are, on average, oriented in a parallel direction. One must then also consider the local polarization field p , which is a vector field giving the average local orientation of

the molecules (DeGennes and Prost, 1993). If an external perturbation is exerted on the orientation of the molecules, the polarization field becomes nonhomogeneous and there is a torque that tends to drive back the molecules in parallel direction. This torque is associated with an orientational field h proportional to the second spatial derivative of the polarization vector. Ignoring again the vectorial character $h = K\Delta p$ where K is a so-called Franck constant and Δ is the Laplacian operator. In a polar liquid, we need to consider both the flow properties and the dynamics of the polarization. The variables that are relevant for the dynamics are then the stress σ and the rate of change of the polarization dp/dt that we identify as fluxes. In a linear hydrodynamic theory, these two fluxes are proportional to the two forces of the problem, which are the orientational field h and the velocity gradient u . Schematically, we write the proportionality relation $\sigma = 2\eta u + \nu h$ and $\partial p/\partial t = h/\gamma + \nu' u$. The coefficient γ is a rotational viscosity associated with dissipation during the rotation of the molecules, and it has dimensions of a viscosity. The two coefficients ν and ν' are in fact related by the Onsager symmetry relations. A simple result of liquid crystal hydrodynamics, which will prove useful below, is the following. Consider a fully polarized liquid where the molecules are all oriented along the z direction. If a simple shear is applied to this liquid with a velocity in the x direction, the amplitude of which varies along z , the molecules are tilted by the shear, and they orient at a finite angle θ_0 from the z direction. The angle θ_0 only depends on the coefficient ν and not on the local velocity gradient.

Actin filaments are polar and have a barbed or plus end and a pointed or minus end (Howard, 2001). Under physiological conditions they tend to polymerize at the plus end and to depolymerize at the minus end. They are also semiflexible as discussed in the “Actin Filaments and Myosin Motors: Mesoscopic Descriptions of the Cytoskeleton” section, and one can therefore build at each point a unit vector defining the local orientation of each filament. By averaging this unit vector in a small volume around each point, one defines a polarization field p , which gives the average local orientation of the actin filaments. For example, at the front edge of the lamellipodium of a crawling cell, the actin filaments are known to make with equal probabilities an angle of $\pm 35^\circ$ with the normal to the edge (Svitkina and Borisy, 1999). The polarization vector is then perpendicular to the edge of the lamellipodium and has a modulus equal to $\cos 35^\circ$. As mentioned above, the specific feature of the lamellipodium is that it consumes energy by hydrolyzing ATP both due to molecular motors and to the actin treadmilling process. In the same spirit as our two previous examples, we must thus now consider three fluxes in the cytoskeleton, the stress σ , the rate of variation of the polarization $\partial p/\partial t$, and the ATP consumption rate r , which is the number of hydrolyzed ATP molecules per unit time and per unit volume. We therefore ignore all details of molecular motors and of the tread-

milling process, and we only retain the fact that ATP is consumed. The “force” conjugate to the ATP consumption rate is the free energy $\Delta\mu$ fueled into the system for each hydrolyzed ATP molecule. By definition, this is the difference between the chemical potential of ATP and its hydrolysis products $\Delta\mu = \mu_{\text{ATP}} - \mu_{\text{ADP}} - \mu_{P_i}$. Note that $\Delta\mu$ increases with the ATP concentration and decreases with the concentrations of adenosine diphosphate (ADP) and inorganic phosphate P_i .

The stress σ in the cytoskeleton must thus depend on the three forces, the velocity gradient u , the orientational field h , and $\Delta\mu$. In a linear hydrodynamic theory, it is a linear combination of the three forces (Kruse *et al.*, 2004, 2005)

$$\sigma = 2\eta u + \nu h - \zeta \Delta\mu. \quad (1)$$

This hydrodynamic description therefore naturally leads to the introduction of an active stress, and the active stress is proportional to $\Delta\mu$. The activity coefficient ζ is a material property of the cytoskeleton, which characterizes both the activity of the motors and the ATP consumption in the treadmilling process (as the viscosity is also a material property of the cytoskeleton). It could be calculated from the microscopic theories outlined in the “Actin Filaments and Myosin Motors: Mesoscopic Descriptions of the Cytoskeleton” section. One must, however, add a word of caution here, it is important at this point that the stress has a tensorial character. Locally, there is a preferred orientation given by the polarization p . This is therefore a principal axis of the active stress, the two other principal axes being the two perpendicular directions, which are equivalent. The active stress has thus different values in the direction of the polarization and in the perpendicular directions. The sign is not imposed by the theory, but a large set of experiments shows that the active stress is contractile in the direction of the polarization and dilative in the perpendicular directions (Takiguchi, 1991). A direct consequence is that a change in the orientation of the polarization induces a change in the active stress: typically for a change in the polarization δp , the change in the active stress is $\delta\sigma = \zeta \Delta\mu \delta p$. This is at the origin of many of the effects that we discuss below. We give in the Appendix the full hydrodynamic equations of an active polar gel showing the tensorial character of the stress and the vectorial character of the polarization.

We have up to now considered the cytoskeleton as a liquid with a finite viscosity η . Long-lived cross-links due to proteins such as α -actinin or filamin can be present in the cytoskeleton and at time scales shorter than the viscoelastic relaxation time τ (which is, in general, related to the lifetime of the cross-links), the cytoskeleton behaves as a solid (Larson, 1988). At time scales longer than τ , the actin gel flows and can be described as a liquid. The description of an actin gel by macroscopic continuum elasticity has, for example, been used to study the motion of the bacterium *Listeria*, which is propelled by the elastic deformation of its actin comet (Prost *et al.*, 2008). The macroscopic theory has

been quite successful and describes quantitatively the actin based motion of systems biomimicking *Listeria* such as plastic beads or oil droplets where actin polymerization promoters have been attached to the surface to allow for the formation of an actin comet. The active liquid hydrodynamic theory that we just described has been generalized to take into account the viscoelasticity of the actin gel using the same symmetry arguments. We do not present here the full hydrodynamic viscoelastic equations of a polar active gel. In the following we use either the liquid limit for the response at long time scales or the elastic limit for the response at short time scale (taking into account the active stresses though).

When combined to the force balance equation, the constitutive equations for an active gel or an active liquid such as Eq. (1) allow for a detailed study of the mechanical properties of the actomyosin cytoskeleton. However, these equations are purely mechanical in the sense that they do not take into account any fluctuation existing in the cytoskeleton or, more generally, in active gels. The noise in active gels has both thermal and nonthermal origins. If the active gel is close to equilibrium, i.e., if the chemical potential difference in the gel $\Delta\mu$ is vanishingly small, the noise in the active gel has thermal origin as in any system close to equilibrium. The amplitude of the thermal noise can be calculated from the linear response of the active gel at thermal equilibrium to external perturbations using the fluctuation dissipation theorem. This has been done explicitly in Basu *et al.* (2008). If the ATP chemical potential difference $\Delta\mu$ is finite, the active gel is a nonequilibrium system and the fluctuation-dissipation theorem is broken as has been shown in the experiments of Mizuno *et al.* (2007). The noise correlations can no longer be calculated from general symmetry arguments and must be determined from a microscopic or a mesoscopic model. An important source of noise is due to the stochasticity of the molecular motors and their processivity. Various models to estimate the noise in the cytoskeleton have been proposed in Lau *et al.* (2003) and Hatwalne *et al.* (2002). Noise has also been studied quantitatively in other active systems such as active membranes, which are another type of active system. A strong characteristic of the active noise, which has been checked for active membrane and could also be true for active gels, is the variation of the noise with the viscosity of the surrounding fluid (Manneville *et al.*, 2001).

SPONTANEOUS FLOW AND INSTABILITIES OF ACTIVE GELS

Before discussing the application of the hydrodynamic theory of active gels to biological problems, it is useful to consider the cytoskeleton as a material satisfying the constitutive equations derived for active gels and to discuss qualitatively its hydrodynamic properties.

The essential property of active gels and liquids is that they tend to flow spontaneously even in the absence of any external pressure gradient. A simple example is that of an

active film on a solid surface for which the anchoring of the actin orientation on the solid and on the free surfaces are different and for which there is no active transport on the solid surface (as there would be in a motility assay). The film is perpendicular to the z direction and has a thickness L . On the lower solid surface, the anchoring of the actin filaments can be such that the filaments are perpendicular to the solid surface (along the z direction). On the upper free surface, we consider an anchoring of the filaments along the x direction as shown in Fig. 1. There is therefore, in the thickness of the film, a gradient of the polarization orientation and thus, a gradient of active stress. The active stress gradient is balanced by the viscous stress, and therefore, there exists a finite velocity gradient in the film: the liquid flows in the x direction, and the velocity varies along the z direction. As for classical nematics under flow, the velocity field tilts the polarization orientation exactly in the same way as the molecules of a classical liquid crystal are oriented in a shear gradient. In the center of the film, the actin filaments are oriented at a fixed angle with the flow that does not depend on the intensity of the flow but only on the material coefficient ν introduced in Eq. (1). Close to the two surfaces of the film, there is a boundary layer where the orientation of the filaments varies to match the anchoring boundary conditions. The order of magnitude of the active stress is $\zeta\Delta\mu$ (as mentioned above, the active stress depends also on the orientation of the filaments). The viscous stress is proportional to the derivative of the velocity $u = \partial v / \partial z$ and is of the order ηu . Equating the viscous stress to the active stress gives, therefore, a velocity on the order of $v \sim L\zeta\Delta\mu / \eta$ proportional to the activity in the system. This flow of the active gel is not due to an external pressure gradient but to the active stresses (related to the action of molecular motors) imposed by the anchoring boundary conditions.

An even more spectacular result is obtained if one considers a similar film with identical boundary conditions on both surfaces, for example, parallel to the surfaces (Voituriez *et al.*, 2005). In this case, there exists an obvious steady state where all filaments are parallel to the surfaces, and the velocity vanishes everywhere. It turns out that if the thickness of the film is large enough, this state is unstable, the polarization has a small nonuniform tilt, and the gradient of polarization induces a flow as we just discussed, which produces itself a tilt of the polarization. If the polarization tilt is δp , the order of magnitude of the active stress is $\zeta\Delta\mu\delta p$. As above, this stress is balanced by the viscous stress and creates a ve-

Figure 1. Sketch of a thin active gel film with different boundary conditions on the solid and free surfaces.

locity gradient $u \sim \zeta\Delta\mu\delta p / \eta$. The equation for the polarization is the same as that given above for a classical liquid crystal $\partial p / \partial t = h / \gamma + \nu' u$ and, in a steady state, the two terms on the right-hand side balance each other. The orientational field h is proportional to the second derivative of the polarization, it is on the order of $h \sim K\delta p / L^2$. We therefore obtain $u \sim K\delta p / (\gamma L^2)$. Comparing the two expressions for velocity gradient u gives the critical thickness for the instability $L_c^2 \sim \eta K / (\gamma \zeta \Delta \mu)$. If the thickness is smaller than the critical thickness L_c , the homogeneous nonflowing state is stable, but if the thickness is larger than the critical thickness (or, equivalently, if the activity is increased at constant thickness above a critical value), the homogeneous state is unstable and the film flows.

The value of the critical thickness for spontaneous flow of the cytoskeleton is difficult to estimate because the bending rigidity K is not known for actin. If we use for K the same value as for simple liquid crystals, we find a critical thickness L_c smaller than $1 \mu\text{m}$. It is not known whether this instability plays any role in the motion of the lamellipodium of motile cells.

A very general and important prediction is that, in most cases, the nonmoving state of an active gel is not stable with respect to a flowing state as long as the length scales involved are larger than L_c . Other flow patterns have been discussed such as vortices or even regular arrays of vortices (Voituriez *et al.*, 2006). Superb examples of rotating vortices created by motor activity have, for example, been observed with microtubules interacting with kinesin motors, which can be considered as another example of active gel (Nedelec *et al.*, 1997).

ACTIVE GEL DESCRIPTION OF CELLULAR PROPERTIES: LAMELLIPODIUM MOTION, CORTICAL ACTIN

We now give two examples of application of the active gel theory to the cytoskeleton. We first discuss the motion of the lamellipodium of keratocyte cells and then cell oscillations associated with instabilities of cortical actin.

Keratocyte motion

A beautiful set of experiments done in particular by the group of Verkhovsky has studied in detail the crawling motion of fish skin keratocytes on a solid surface (Verkhovsky *et al.*, 1999). The front part of an advancing keratocyte cell is a very flat lamellipodium with a thickness on the order of a micrometer. The lamellipodium is mostly constituted of actin filaments and of myosin motors, and it can be described by the active gel theory. The cell body containing the cell machinery is at the back of the cell and is pulled by the lamellipodium. One of the spectacular experimental results is that the actin velocity field is retrograde (Vallotton *et al.*, 2005): if the whole cell advances with velocity U to the left, the actin flow is to the right and

decays toward the back of the cell over a length d . The advancing cell velocity if on the order of $10 \mu\text{m}$ per minute and the actin velocity v is much smaller on the order of $1 \mu\text{m}$ per minute. The tangential stress profile on the substrate σ_t has also been measured directly, and values on the order of 10^2 Pa have been obtained (Oliver *et al.*, 1999). We define here all velocities in the laboratory reference frame. Assuming that the velocity does not vary much over the thickness of the lamellipodium, we define a friction constant per unit area by $\sigma_t = \xi v$. This friction constant is on the order of $\xi \sim 10^{10} \text{ Pa s m}^{-1}$, which is the same order of magnitude as the friction coefficient per unit area measured in experiments on actin based propulsion (Prost *et al.*, 2008). A sketch of an advancing lamellipodium is given in Fig. 2.

The local force driving the actin flow is due to the stress σ in the direction of motion; the local force per unit area of the lamellipodium in the direction x of motion is obtained by integration over the thickness h of the lamellipodium, and it is equal to $h(d\sigma/dx)$. The viscous force per unit area in the lamellipodium is therefore $\eta h(d^2v/dx^2)$. The velocity varying over a length d , the viscous force is of the order $\eta h(v/d^2)$. The length d is obtained by writing that the viscous force is balanced by the friction force on the substrate, leading to $d \sim (\eta h/\xi)^{1/2}$. Using the previous orders of magnitude, we find a friction length $d \sim 6 \mu\text{m}$ of order half the length of the lamellipodium. The amplitude of the actin velocity at the edge is obtained by writing that the active stress $\zeta\Delta\mu$ is on the order of the viscous stress $\eta v/d$, or $v \sim d\zeta\Delta\mu/\eta$. If we use the experimental value $v \sim 1 \mu\text{m}$ per minute, we estimate the active stress as $\zeta\Delta\mu \sim 10^3 \text{ Pa}$. This is to be compared to the shear modulus of the actin gel $E \sim 10^4 \text{ Pa}$. A detailed calculation of the velocity distribution, of the local force, and of the shape of the lamellipodium has been done in Kruse *et al.* (2006). We give the corresponding plots in Fig. 3.

The actin velocity in the lamellipodium is thus driven by the actomyosin contractility. The advancing velocity is driven by the actin treadmilling process. The experiments of Verkhovsky *et al.* (1999) show that actin polymerizes at the edge of the lamellipodium and depolymerizes in the bulk of the lamellipodium or at the rear. The detailed study of Kruse *et al.* (2006) shows that the advancing velocity U is

Figure 2. Sketch of a lamellipodium advancing on a solid substrate. The lamellipodium is advancing to the left at a velocity U . It is connected to the cell body on the right. The thickness h increases with x and is roughly constant in the central part of the lamellipodium.

Figure 3. Calculated velocity, force, and height profiles of a thin active gel layer corresponding to a lamellipodium which is moving on a substrate in the negative x -direction with velocity $u=10 \mu\text{m}/\text{min}$. The position x is measured along the horizontal axis and given in micrometers. The flow velocity v of the gel layer relative to the substrate is given in micrometers per minute, and the gel thickness h is given in micrometers. The integrated stress across the active gel layer F is given in units of $0.5 \text{ nN}/\mu\text{m}$. The parameter values are $\zeta\Delta\mu/4\eta=-0.21/\text{min}$, $\xi/4\eta=1/(36 \mu\text{m})$, and $u=10 \mu\text{m}/\text{min}$. Furthermore, we use $\xi=3 \cdot 10^{10} \text{ Pa s/m}$ and $k_{p\text{wa}}^0=9 \mu\text{m}/\text{min}$.

approximately equal to the depolymerization velocity at the rear, and therefore, that it is dominated by the actin treadmilling process.

Note that we considered so far the actin cytoskeleton as a pure liquid. The actin filaments polymerizing at the front treadmill toward the rear of the lamellipodium. Actin only flows after the viscoelastic relaxation time τ . There is therefore a region at the tip of size $U\tau \sim 1 \mu\text{m}$ where actin cannot be considered as a fluid but must be considered as a solid, which flows as a block with a constant velocity. The interaction of actin with the cell membrane plays then an important role discussed for cilia by Prost *et al.* (2007), Mogilner and Rubinstein (2005), Atilgan *et al.* (2006), and Gov (2006).

Despite the many oversimplifications involved, the active gel theory gives a good qualitative description of an advancing lamellipodium and, in particular, it explains the observed actin retrograde flow. It also allows estimating the physical parameters associated with the cytoskeleton and, in particular, of the active stress $\zeta\Delta\mu$. The only other type of cells that we are aware of where a similar analysis can be done are neural growth cones. Both the velocity field and the friction force have been mapped by the group of Kaes (Betz *et al.*, 2006), and the active stress can be estimated using the procedure applied to the keratocyte cell. One finds an active stress $\zeta\Delta\mu \sim 50 \text{ Pa}$ smaller than for the keratocyte, but in this case the measured elastic modulus of the actin cytoskeleton is smaller and the ratio $\zeta\Delta\mu/E$ is of the order 0.5.

Although the hydrodynamic theory of active polar gels gives a qualitatively good description of the retrograde flow and of the shape of the lamellipodium in simple terms and with very few adjustable parameters (essentially the activity coefficient) it is, of course, an oversimplification and ignores several features such as the many proteins that interact with

actin for capping, cross-linking, severing ... A good review of the various components of the lamellipodium is given in [Small *et al.* \(2002\)](#). Several models have discussed the effect of these proteins ([Schaub *et al.*, 2007](#); [Schaub and Borisy, 2008](#); [Huber *et al.*, 2008](#)).

Cortical actin

In many cells actin is located at the cortex just below the membrane where it interacts with molecular motors ([Charras *et al.*, 2005](#)). The cortical actin layer can therefore be considered as an active gel. The mechanical properties of this gel have a strong influence on the morphology of cells and in particular on some shape instabilities of cells such as blebbing or spontaneous oscillations ([Paluch *et al.*, 2005](#); [Pletjushkina *et al.*, 2001](#)). Recent experiments in [Salbreux *et al.* \(2007\)](#) show that when fibroblasts do not adhere, they can spontaneously oscillate. Biological tests show that the oscillations are dependent on the activity of the cortical layer and on the external calcium concentration.

In the cortical actin layer, actin polymerizes at the membrane, almost parallel to the cell surface but with a random orientation. The application of the active gel theory to the cortical actin layer shows then that the cortical layer can be characterized by an effective tension, which is the product of the active stress $|\zeta\Delta\mu|$ and its thickness e . Using the previous orders of magnitude for the active stress and a thickness on the order of $1\ \mu\text{m}$, one obtains a tension on the order of $10^{-3}\ \text{N m}^{-1}$ larger than the membrane tension. A stability analysis of the cortical layer shows that it can be unstable with respect to thickness fluctuations if the activity is large enough, but that this instability does not lead to oscillations. In order to explain the shape oscillations, one has to hypothesize the existence of gated calcium ion channels coupled to the cortical layer. If the channels are open, calcium enters the cell and increases the activity of the myosins, therefore increasing the contraction of the cortex. The tension increase leads to a contraction of the cell and to a closure of the channels. Calcium is then evacuated by pumps, the activity decreases, and the calcium channels open again. This provides a basis for an oscillatory instability, which is coupled to a deformation of the cell as observed experimentally. Detailed calculations show that the period of the oscillations actually decreases with the activity as observed experimentally.

Other instabilities of cells such as the formation of blebs or cell instabilities upon depolymerization of the microtubules ([Paluch *et al.*, 2005](#)) are also currently being studied by using the hydrodynamic theory of active gels to describe the mechanical properties of the actin cortex. The onset of cytokinesis and cortical actin wound healing can also be studied by the same formalism. More generally, an important set of problems not discussed in this review are all the questions associated with the regulation of the cytoskeleton by the membrane shape due to a feedback mechanism between cytoskeletal forces and membrane shape.

DISCUSSION

In this short review we have presented qualitatively a systematic way to construct a hydrodynamic theory to describe the mechanical properties of the cytoskeleton. The main advantage of this approach is that it characterizes the properties of the cytoskeleton by a small set of phenomenological parameters. Most of these coefficients have already been introduced in the physics of classical complex fluids such as polymeric liquids for the viscoelasticity or liquid crystals for the parameters related to the polarization. The main new feature of the cytoskeleton is that it is an active system driven by ATP consumption. In the simplest cases, activity introduces one new parameter, the activity coefficient ζ . Qualitative or semiquantitative comparison to experiments such as the ones on lamellipodium motion give an order of magnitude of this coefficient and of the associated active stress. The activity leads to spectacular and nonintuitive behaviors as illustrated by the flow instabilities discussed in the “Spontaneous Flow and Instabilities of Active Gels” section. One of the difficulties of the hydrodynamic approach is that one has to understand how the phenomenological parameters change with the biological conditions, i.e., to figure out how the changes in the expression of a given protein affect these parameters. An increase in the number of molecular motors, for example, clearly leads to an increase of the activity coefficient ζ . A naive model would predict a linear increase with the concentration of molecular motors. One has to be aware, however, that other parameters could change with the myosin concentration and that increasing the expression of myosins could lead to a complex path in the parameter space.

One of the major experimental challenges now is to build active polar gels in a situation where all physical parameters are well controlled allowing for quantitative tests of the predictions of the hydrodynamic theory ([Bendix *et al.*, 2008](#)). There seems to be two ways to approach this question: either to study actin myosin complexes *in vitro* in controlled conditions and controlled geometries (microfluidic environments could turn out to be very useful for that) or to build up purely synthetic chemical systems which share the main features as active polar gels, polarity, viscoelasticity, and energy consumption associated with the active character. This would lead to a completely new class of materials with very unusual properties.

On the more biological side, even for actin-myosin systems, which are extensively studied, many of the physical constants that we introduced are not known precisely. One of the difficulties is that the theory that we presented is a linear theory in the sense that it implicitly assumes that the ATP chemical potential difference $\Delta\mu$ is small and that all the physical parameters only have small variations around their average values. A typical example is the activity coefficient ζ . In the linear theory, it has a constant value. However, it is known that the myosin density in a lamellipodium is very nonhomogeneous, it is larger at the back and smaller at

the front. One could then expect a strong variation of ζ between the back and the front of the lamellipodium. A second example is the variation of the actin cytoskeleton properties with the ATP concentration. In the theory presented here, all active properties are proportional to $\Delta\mu$, i.e., to $\log c_{\text{ATP}}$, where c_{ATP} is the ATP concentration. There are, of course, strong nonlinear effects and a detailed theory of molecular motors such as the two-level model of [Julicher et al. \(1997\)](#) that predicts a velocity and a stall force of the motors that does not increase linearly with $\Delta\mu$. One would therefore need a nonlinear hydrodynamic theory of active gels. There does not seem to be any systematic way to construct such a theory, and the pragmatic approach, which consists to introduce specific nonlinear features in the linear theory based on experimental observations or on microscopic theories, is the most efficient way to obtain an accurate description of the experiments.

One of the main advantages of the linear active gel theory is that it is not based on any microscopic assumptions or modeling. The structure of the equations is only based on symmetries. The only assumption is the choice of a model to describe the viscoelasticity. For the sake of simplicity, we chose here the Maxwell model, which postulates that the stress has a single relaxation time. It has been shown experimentally that it is not actually the case for the actomyosin cytoskeleton, and the theory will have to be modified to take into account the distribution of relaxation times ([Fabry et al., 2001](#)). However, this choice of the relaxation dynamics being made, the rest of the theory is imposed by symmetry arguments. The theory is therefore generic and can be used to describe any physical system which shares the same symmetries as the actomyosin cytoskeleton.

Among the biological systems that one can describe using a very similar hydrodynamic approach one can think of bacterial colonies or cellular tissues. Colonies of bacteria consume energy in the form of oxygen, and the individual bacteria are polar; they always advance in the same direction. Two dimensional bacterial colonies at the bottom of a water drop have been observed to have very unusual flow patterns with many disordered eddies looking much like turbulent flow patterns even though the Reynolds number is extremely low ([Tuval et al., 2005](#)). The theories that have been proposed for this bacterial turbulence are very similar to our active gel theory. And the eddies are instabilities of the colony similar to those discussed in the “Spontaneous Flow and Instabilities of Active Gels” section.

Cellular tissues are also active systems where the cell polarity plays a major role ([Shraiman, 2005](#); [Hufnagel et al., 2007](#)). One can, in the same spirit as the one presented here, build up a hydrodynamic theory to describe tissue dynamics. This opens the way to a whole range of questions on tumor growth as well as organ growth during development. This also raises several questions on the coupling between the mechanical properties of the tissue, cell division, and cell death

(apoptosis) or on stress relaxation in tissues, which could have a liquidlike or a solidlike behavior. One would also need to relate the macroscopic properties of the tissue to the properties of the individual cells and to the interactions between cells (cell adhesion) that are themselves described by the active gel theory of the cytoskeleton.

APPENDIX: HYDRODYNAMIC THEORY OF ACTIVE POLAR GELS

In this appendix, we give the full hydrodynamic equations of an active polar gel as derived by [Kruse et al. \(2005\)](#). For the sake of simplicity, we consider only an incompressible gel. The three thermodynamic forces are the symmetric part of the velocity gradient $\tilde{v}_{\alpha\beta} = \frac{1}{2}(\partial v_\alpha / \partial r_\beta + \partial v_\beta / \partial r_\alpha)$, the orientational field h_α , and the free energy released by the hydrolysis of one ATP molecule $\Delta\mu$.

The total stress $\sigma_{\alpha\beta}^t$ is not symmetric in a polar material and must be written as a sum of a symmetric and an antisymmetric part. As for nematic liquid crystals, the antisymmetric part, which is the local torque, is obtained from the conservation of kinetic momentum and is equal to

$$\sigma_{\alpha\beta}^a = \frac{1}{2}(p_\alpha h_\beta - p_\beta h_\alpha). \quad (2)$$

The symmetric component of the stress is the sum of the pressure and of a traceless deviatoric stress tensor $\sigma_{\alpha\beta}$. The three fluxes conjugate to the forces are the symmetric part of the stress $\sigma_{\alpha\beta}$, the rate of change of the polarization $P_\alpha = Dp_\alpha / Dt$, and the number of ATP molecules consumed per unit time and per unit volume r . In order to satisfy rotational and translational invariance, the rate of change of the polarization must be defined using the corotational time derivative $(D/Dt)p_\alpha = \partial p_\alpha / \partial t + (v_\gamma \partial_\gamma p_\alpha + \omega_{\alpha\beta} p_\beta)$, where $\omega_{\alpha\beta}$ is the antisymmetric part of the velocity gradient (the vorticity tensor). The complete derivation of the constitutive equations is based on an explicit calculation of the entropy production, which shows that the fluxes and the forces are indeed conjugate variables in the thermodynamic sense. The constitutive equations read

$$2\eta v_{\alpha\beta} = \left(1 + \tau \frac{D}{Dt}\right) \left\{ \sigma_{\alpha\beta} + \zeta \Delta\mu q_{\alpha\beta} + \tau A_{\alpha\beta} - \frac{\nu_1}{2} \left(p_\alpha h_\beta + p_\beta h_\alpha - \frac{2}{3} h_\gamma p_\gamma \delta_{\alpha\beta} \right) \right\}, \quad (3)$$

$$\frac{D}{Dt} p_\alpha = \frac{1}{\gamma_1} h_\alpha + \lambda_1 p_\alpha \Delta\mu - \nu_1 v_{\alpha\beta} p_\beta - \bar{\nu}_1 v_{\beta\alpha} p_\alpha, \quad (4)$$

$$r = \Lambda \Delta\mu + \zeta p_\alpha p_\beta v_{\alpha\beta} + \bar{\zeta} v_{\alpha\alpha} + \lambda_1 p_\alpha h_\alpha. \quad (5)$$

We have introduced in these equations the quadrupolar tensor $q_{\alpha\beta} = p_\alpha p_\beta - \frac{1}{3} p^2 \delta_{\alpha\beta}$. The various transport coefficients are defined in the main text.

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