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Mechanics and polarity in cell motility

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ABSTRACT

The motility of a fish keratocyte on a flat substrate exhibits two distinct regimes: the non-migrating and the migrating one. In both configurations the shape is fixed in time and, when the cell is moving, the velocity is constant in magnitude and direction. Transition from a stable configuration to the other one can be produced by a mechanical or chemotactic perturbation. In order to point out the mechanical nature of such a bistable behaviour, we focus on the actin dynamics inside the cell using a minimal mathematical model. While the protein diffusion, recruitment and segregation govern the polarization process, we show that the free actin mass balance, driven by diffusion, and the polymerized actin retrograde flow, regulated by the active stress, are sufficient ingredients to account for the motile bistability. The length and velocity of the cell are predicted on the basis of the parameters of the substrate and of the cell itself. The key physical ingredient of the theory is the exchange among actin phases at the edges of the cell, that plays a central role both in kinematics and in dynamics.

0. Introduction

The motility of eukaryotic cells on flat substrates is conventionally described according to four phases: leading edge protrusion, adhesion to the substrate, contraction at the trailing edge and then retraction of the tail [1]. This scenario is however only stereotypical because for some cells, like fish keratocytes, these phases follow each other so rapidly that they are actually undistinguishable: all the steps occur simultaneously and the translation process is continuous in time. Moreover fish keratocytes exhibit two distinct motile regimes: in absence of external stimuli, they typically stay at rest with a rounded shape. A sufficiently large mechanical or chemotactical signal can trigger a destabilization that, in about 200 s, yields the cell to travel with constant velocity (up to 1 μm s^{-1}) and shape [2]. The same kinematics even characterizes the motion of a fragment of cell lamellipodium, with a lower speed ($\simeq$2–10 μm per minute); as it lacks nucleus, microtubules and most organelles, the experiment suggests that the key elements of cell crawling are well represented even in such a simple system. The exhibited bistable behaviour, signature of a nonlinear dynamics, is a fascinating challenge for the mathematical modelling of an active living mechanical system.

Both when the cell (or the lamellipodial fragment) is apparently at rest and when it is steadily migrating, the inner equilibrium of the mechanical system is actually dynamical: at a subcell level, the flow of free and polymerized actin follow patterns that have been unravelled during the last decades [3,4]. Oligomeric actin (G-actin) freely diffuses in the cytosol and attaches to the barbed ends of the polymeric phase network (F-actin) that point outward the cell membrane; polymerized actin is backward transported by the myosin motors (retrograde flow). The vectorial sum of material velocity and growth velocity (polymerization rate) at the cell boundary produces the visible speed of the cell (which is possibly null). Free actin monomers detach from the actin network in the body of the cell and are passively transported by Brownian motion from regions of higher to regions of smaller concentration (namely the cell periphery, where the polymerization process acts as a sink for the G-actin) [5]. The free actin density correlates well with the high stress regions inside the cell, inhibition of the stress due to myosin activity slows down the cell, thus suggesting that the mechanical stress drives the depolymerization process [6,7].

The shape of the boundary and the concentration patterns are very different between crawling and non crawling fragments. The fragment at rest is rounded, the lamellipodium has a symmetric shape, the actin cytoskeleton near the membrane grows at a constant rate and is backtransported from the boundary to the interior at the same velocity it is produced, so that the vectorial sum of velocities is zero. In a travelling fragment, the lamellipodium takes instead a characteristic canoe shape, the

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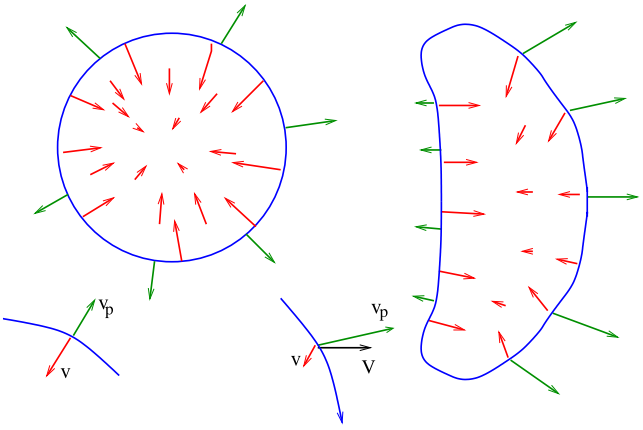

Fig. 1. Velocity pattern in a fish keratocyte at rest (left) and in a migrating one (right) (sketch from figure 1 in [7]). In the cell at rest, the material velocity v (in red) balances the growth velocity v_p (in green) at the boundary; in a migrating cell the sum of the contributions imbalance at the boundary and gives rise to the steady motion with velocity V which is the vectorial sum of the two contributions [8]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

symmetry of actin and myosin concentration patterns is broken and the region of strong actomyosin activity is concentrated in the rear of the lamellipodium (see Fig. 1).

The polarization of the cell and the initiation of motility is strongly linked to the migration of several proteins on the plasma membrane and their spatial segregation. In particular, Rho GTPases are of crucial importance in regulating actin dynamics at the cell periphery [9]. Actin nucleation is typically the rate-limiting step in actin polymerization in vivo, so cells regulate where and when polymerization occurs by controlling the localization and activation of actin-nucleation promoting factors [10]. The polarity of the network is therefore instructed by the polarization of the membrane.

The mathematical modelling of cell migration has received an increasing attention over the last years. The evidence of a bistable behaviour is the signature of a nonlinearity that has been encoded in the models in terms of nonlinear constitutive equations for the cellular material. Alt and Dembo [11] and Kimpton et al. [12] represent a cell as made of biphasic material, where the stress of the network has a spherical component which is cubic in the volume fraction. The nonlinearity of the constitutive equations determines the multiplicity of the stable regimes. According to Giomi and De Simone [13] a cell described as an active nematic droplet undergoes spontaneous division and motility thanks the phase separation favoured by the Ginzburg–Landau energy density and the nonlinearity of the Landau–deGennes free energy density. The theoretical aspects of cell motility can be addressed after homogenization of equations that detail the dynamics of the actin network, each filament being treated as an inextensible rod that resists to bending. Branching, capping, cross links and friction of the filaments of the network can be very naturally included in such a modelling framework [14]. Other approaches focus on the contraction-driven motility in a 1D cell: recent theoretical works based on the theory of active gels show that crawling is possible even without polymerization [15]. This particular mechanism of cell motility allows a precise formulation of the condition of optimal trade-off between performance and metabolic cost, so that the distribution of contractile elements can be recovered on the basis of an optimization argument [16]. The region at the leading edge, where the branched F-actin network is not stabilized by cross links, is very narrow when compared with the typical length of the lamellipodium: a few hundreds nanometres vs. 10 μm [17]. An accurate mathematical modelling of such a flexible region is needed to get rid of the force–velocity relationship observed when a cell migrates on a flat substrate pushing a bending cantilever [18].

The mathematical model illustrated in this paper is inspired by Mori et al. [19] and Larripa and Mogilner [20,21], where the protein recruitment and segregation in the cytosol and on the membrane, the mechanics of the cytoskeleton and the treadmilling of actin are separately addressed. Here we formulate a minimal 1D theoretical model where the observed dynamics of free and polymerized actin in the cell is coupled with the stress actively produced by the myosin motors. The polarization of the cell follows the "wave pinning" model; the linear diffusion of proteins (namely Rho GTPases) on the plasma membrane and in cytosol and the nonlinear exchange between active (membrane-bound) and inactive (cytosolic) forms explains the existence of polar and non-polar stable states, while the (reversible) transitions among such states of the system occurs by finite perturbations [19]. The formation of a stationary front (the "wave pinning"), sharply separating the cell into two regions, mechanically identifies the polarity of the F-actin network, where barbed ends do not point out of the cell in a radially symmetric way, but mostly in the direction of the motion. The novelty of our work is the focus on the mass conservation and momentum balance laws of the actin phases, supplemented by mass exchange and boundary flow, that all the components of the system must satisfy. While bistability is governed by diffusion and exchanges of proteins, we mechanically enforce the polarity of the cell in the boundary condition for the F-actin, relating its concentration to local amount of active proteins. The linearity of the constitutive equations allows to analytically compute stress and concentration fields, that are qualitatively in agreement with the observations. Our main result is the quantitative prediction of the length and the migration velocity of the cell fragment in the two stable configurations (cell at rest and motile cell) as a function of the physical parameters of the model.

1. The mathematical model

The lamellipodium of a fish keratocyte is a very thin structure, less than 1 μm thick vs. a width and a length of about 10–20 μm [22]. The shape of a cell at rest is almost cylindrical, while the shape of a steadily migrating cell exhibits a symmetry axis in the plane. Symmetry arguments and the corresponding high aspect ratios suggest to represent the cell as a one-dimensional strip, spanning the interval $(x_-(t), x_+(t))$ of the x axis, where the location of the boundaries is to be determined. In the following, all the relevant physical fields are therefore to be understood as averaged along the vertical and transverse direction.

The onset of polarity in a cell is due to membrane trafficking of a number of proteins. A minimal mathematical model able to capture the essential dynamics is provided by two reaction–diffusion equations for a protein (Rho GTPases, for example) that diffuses with different rates on the membrane and in cytosol [19]

$$\begin{aligned} u_t - D_u u_{xx} &= f(u, w), \\ w_t - D_w w_{xx} &= -f(u, w), \end{aligned} \tag{1}$$

where $u(x, t)$ and $w(x, t)$ represent the concentration on the membrane and in the cytosol, respectively, $D_u \ll D_w$, and $f(u, w)$ is typically cubic in u. An elementary non-dimensional example is

$$f(u, w) = (u - u_0)(u - u_1)(u - u_2(w + 1)), \tag{2}$$

where $u_2 > u_1 > u_0 > 0$ are constants. Both phases cannot outflow the cell membrane

$$-D_u u_x\big|_{x_\pm} = -D_w w_x\big|_{x_\pm} = 0. \tag{3}$$