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Supplementary Materials for

Stick-slip dynamics of cell adhesion triggers spontaneous symmetry breaking and directional migration of mesenchymal cells on one-dimensional lines

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Supplementary Text

A physical model based on minimal ingredients can capture the observed stochastic stick-slip behavior. The actin cytoskeleton is described in an 1D geometry as an active viscoelastic gel, which we assume is homogeneous and isotropic. No pre-existing polarization mechanism of the cell cytoskeleton is therefore hypothesized. We assume that the cell body behaves as an elastic component of stiffness *k* and induces a restoring force proportional to the cell elongation *x*. This restoring force encompasses both passive and active elastic contributions. The interaction with the substrate can be modeled generically in the framework of active gel theory by assuming that actin polar order is imposed at both cell boundaries (e.g. pointing outwards), for example by actin polymerization factors. Polar order $\boldsymbol{p}=p\,\boldsymbol{u_p}$ then decays exponentially from the cell boundary, with a characteristic length that we assume here small. We identify this polarized region at the boundary with adhesion sites. We determined the thin peripheral polar region with adhesion sites. *p* therefore measures the adhesion strength and $\boldsymbol{u_p}$ is the outward pointing unit vector. For symmetry reasons, active interactions forces between the substrate and the cell cytoskeleton can then be written $\boldsymbol{F_a}=\chi\,\boldsymbol{p}$, where χ is a phenomenological coupling constant. The key ingredient of the model then relies in the dynamics of adhesion sites, which we write phenomenologically as

$$\dot{p} = g(v_p) - \lambda p \tag{1}$$

Here λ models the rate of actin turnover, and g the dynamics of adhesion sites assembly that depends on the local velocity $v_p = v \cdot u_p$ over the substrate. Importantly g is a priori asymmetric and can be written at small *v*: $g(v_p) = \alpha\left(1 - \frac{v_p}{v_+}\right), v_p > 0$; $g(v_p) = \alpha\left(1 + \frac{v_p}{v_-}\right), v_p < 0$, where $v_+ > v_-$ are positive constants that control the dependence of adhesion dynamics on velocity (**Fig. 2D**). This functional form accounts for the fact that adhesion assembly is drastically reduced upon edge retraction, and mildly affected by edge expansion. In turn, α stands for the maximal growth rate of adhesion. It will be useful to consider the maximal contractile force $\frac{\chi\alpha}{\lambda}$. In addition we assume a linear friction of coefficient x between the cell bulk (where *p*=0) and substrate. Force balance then leads to the following dynamics for the variables *X* (cell center of mass) and cell elongation *x*

$$\ddot{X} + \lambda\dot{X} = \frac{\chi}{2\xi}\left(g(\dot{x} + \dot{X}) - g(\dot{x} - \dot{X})\right) \tag{2}$$

$$\ddot{x} + (\lambda + \mu)\dot{x} + \lambda\mu x = \frac{\chi}{2\xi}\left(g(\dot{x} + \dot{X}) + g(\dot{x} - \dot{X})\right) \tag{3}$$

where $\mu = \frac{k}{\xi}$. The analysis of this non linear system shows that the fixed point $\dot{X} = 0, x = \chi\alpha/(k\lambda)$ (non moving cell) is unstable if

$$\frac{\chi\alpha}{\lambda\xi v_-} > 1 + \frac{\mu}{\lambda} \tag{4}$$

This shows that, assuming $v_- < \frac{\chi\alpha}{k}$ (strong enough dependence of adhesion dynamics on speed), the dynamics is controlled by the turnover rate λ. In particular at slow turnover rates (as defined by Equation 4), the system displays a stochastic stick-slip behavior, which differs from classical stick-slip behaviors with deterministic oscillations: the fixed point is indeed unstable for $v_p < 0$, but stable for $v_p > 0$. Deterministic trajectories therefore relax in infinite time to the fixed point and correspond to slowly expanding cells with no stick-slip. However, close to the fixed point, any fluctuation leading to infinitesimal retraction is unstable: one end of the cell therefore retracts before spreading symmetrically again. In the presence of noise, the system therefore undergoes stick-slip cycles of asymmetric retraction of one cell end and symmetric expansion that are triggered randomly. At large time scales, the cell therefore performs a random walk. In the limit of slow turnover rate λ, adhesion dynamics and therefore scales control the period of each cycle as $1/\lambda$, while the cell moves typically of one cell length. Importantly, this migration mechanism does not require any polarization mechanism of the cell cytoskeleton: front-back symmetry is broken only in the adhesion dynamics. In contrast, in the limit of large turnover λ (or small maximal contractile force $\frac{\chi\alpha}{\lambda}$), the fixed point is stable, and no stick-slip motion occurs. In that case the breaking of the front-back symmetry requires another mechanism, such as a contractile instability of the actin cytoskeleton, which we do not aim at describing here. Finally, the model successfully reproduces the observed stochastic stick-slip dynamics (**Fig. 2G**), and predicts that it is critically controlled by adhesion turnover rate λ and maximal contractile force $\frac{\chi\alpha}{\lambda}$, as summarized in the phase diagram of **Fig. 2F**.

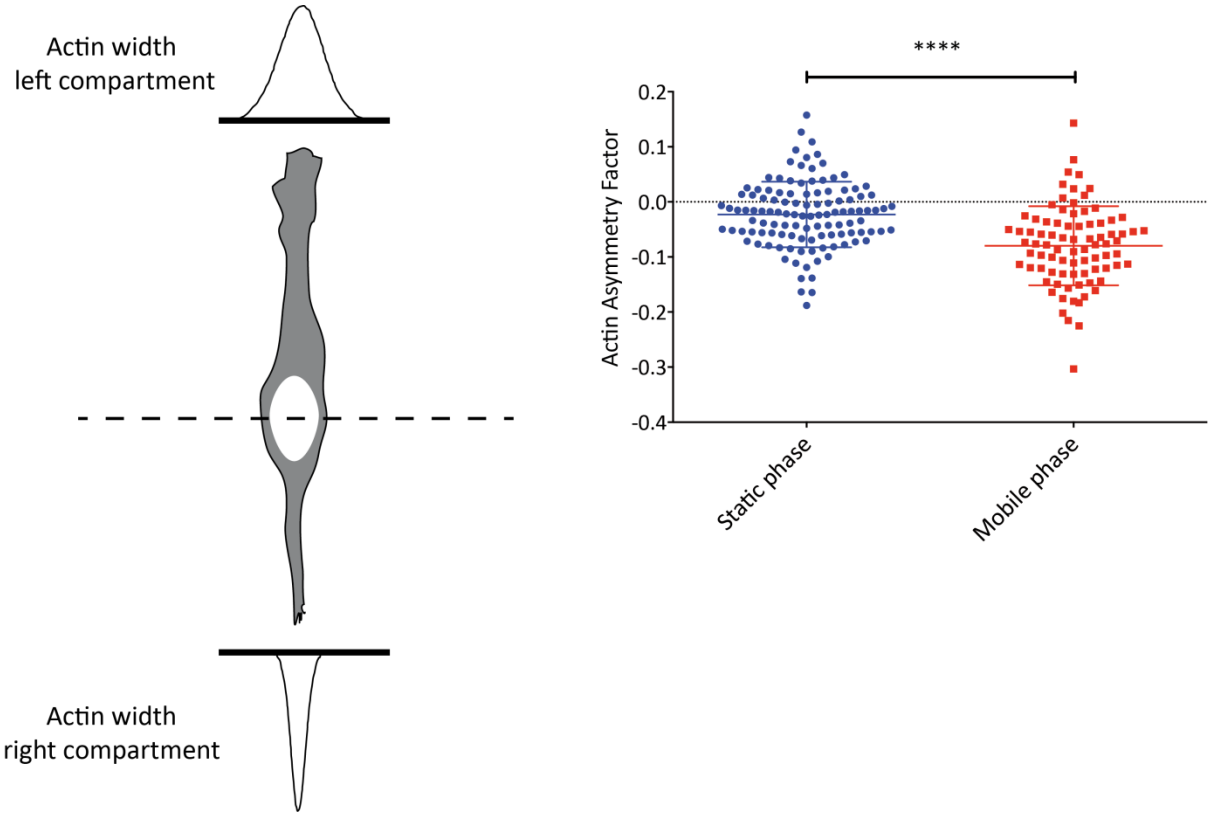

Fig. S1. Polarization of the actin cytoskeleton. Schematic representation depicts the actin asymmetry factor calculation, which was based on the comparison of the actin distribution of either cell side. The quantification reveals a symmetric distribution during static phases. This symmetry is broken when cells moves. Statistical significance tested with unpaired t-test ($P < 0.05$), error bars on graphs show standard deviation from the mean ($n = 10$ cells).

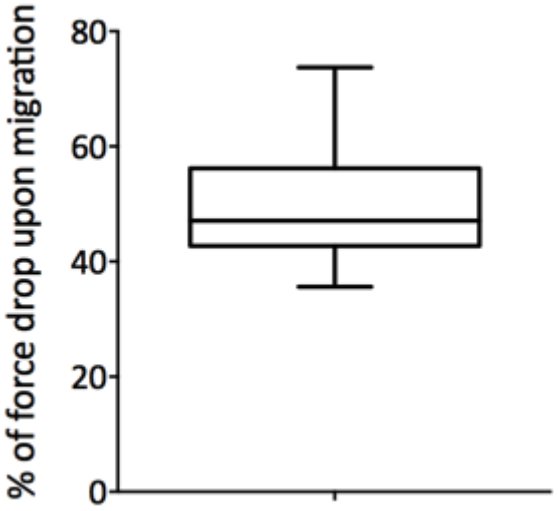

Fig. S2. Mechanical interaction between the cell and its environment decreases upon the initiation of migration. Relative drop of the total traction forces of single cells. ($n = 10$ cells)

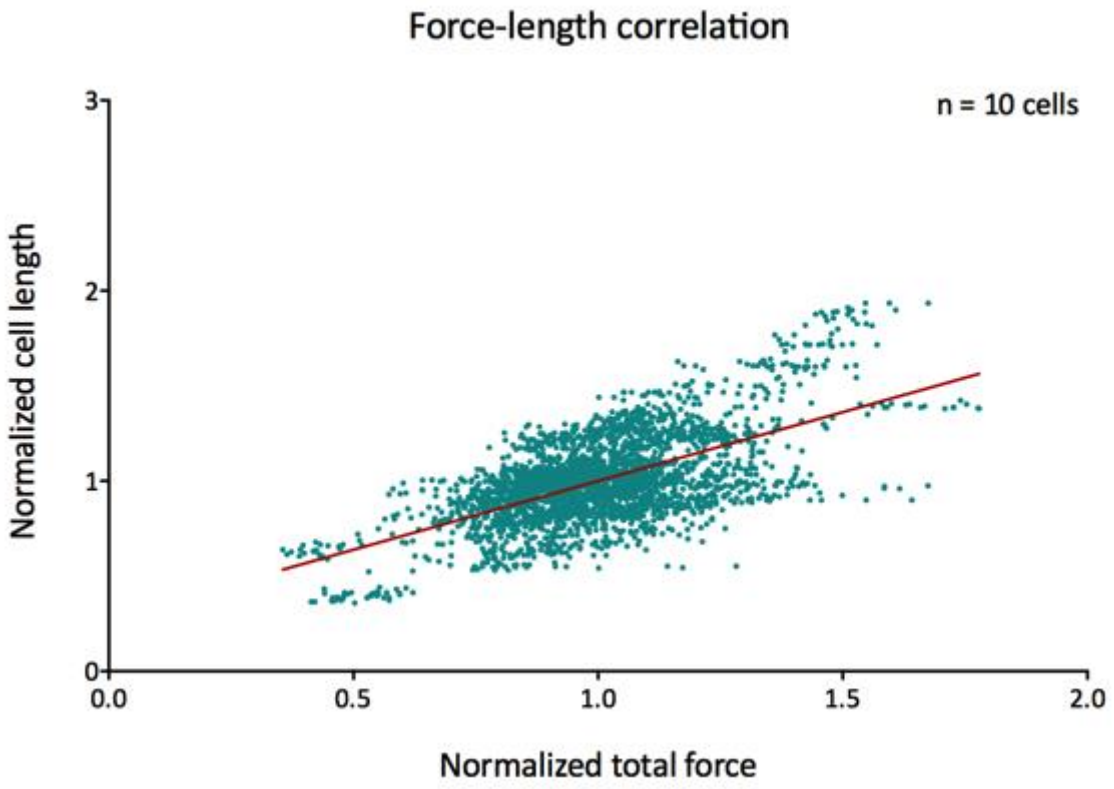

Fig. S3. Force-length correlation during stick-slip migration. Cells during stick phases elongate while increasing their mechanical interaction with the substrate. Upon initiation of migration (slip phase), both cell length and total force level drop due to the detachment of the rear. Blue: normalized instantaneous cell length and total force during a single cell's migration trajectory. Red: Linear fit.

Movie S1. Adhesion dynamics of RPE1 and NIH-3T3 cells. TIRF imaging of stably expressed vin-eGFP quantitatively revealed a fast adhesion turnover for fast migrating RPE1 cells compared to slow migrating NIH-3T3 cells. Adhesion patches for RPE1 slide and disassemble with the retracting rear, while NIH-3T3 cells rapidly reattach their back adhesions.