I. Mathematical simulations of cell trajectories

For simplicity in our simulations to describe the large scale effects of angular variation on cell trajectories, we decompose each cell's trajectory in two-dimensional space to a set of vectors, $\vec{v}$, of fixed magnitude, v, but variable angle, θ. Of note, the assumption of fixed magnitude is not crucial as long as there is not a significant relationship between $\delta\theta$ and v. We can consider three simple sources of variation in θ: (A) a randomly chosen value of θ at each time point where $\theta\epsilon[0, 2\pi)$, (B) a randomly chosen angular velocity, ω, at each time point from a normal distribution where $\omega \sim \mathcal{N}(\mu_\omega, \sigma_\omega^2)$, (C) a randomly chosen change in angular velocity, $d\omega/dt$, at each time point where $d\omega/dt \sim \mathcal{N}(\mu_{(d\omega/dt)}, \sigma^2_{(d\omega/dt)})$. Simulated trajectories for each of these models are presented in Figure S1C.

Model A represents a uniform distribution of possible angles, creating trajectories that resemble a classic random walk. Variation of this model have been used successfully to describe the motion of *Paramecium* [1] and the running and tumbling motion of *Escherichia coli* [2]. However, as expected such models do a poor job of qualitatively replicating the persistence over time of keratocyte trajectories or quantitatively reproducing the observed distribution in angular speeds, and auto-correlations in angular speed.

To take into account path persistence, established by the persistence of the polarized lamellipodia [3], Model B incorporates a simple correlated random walk in the direction of travel over time, with

$$\theta_i = \theta_{i-1} + \omega * dt, \quad where\ \omega \sim \mathcal{N}(\mu_\omega, \sigma_\omega^2).$$

We have defined μ_ω as 0 and σ_ω^2 as 1 deg $/s^2$ for these simulations. This simple simulation produces trajectories that are wandering in nature. Models of this type have been highly effective in describing the motion of *Dictyostelium discoideum* where the angle of motion from one time point to the next is correlated due to coupling of future protrusion to sites of previous protrusion [4, 5], as well as the movement of other tissue culture cell lines [6].

Qualitatively these wandering trajectories are similar to a subset of the observed keratocyte trajectories. These models also are able to replicate the appropriate distribution of angular speeds, however they fail to recreate the persistent turning behavior that is intermittently exhibited by keratocytes as quantitatively observed by the elevated auto-correlations in angular speed for some cells.

Model C explicitly introduces this correlation between angular speeds, such that the change in direction traveled at one time point is related to the

change in direction traveled at the next time point,

$$\omega_i = \omega_{i-1} + (d\omega/dt) * dt, \quad where\ (d\omega/dt) \sim \mathcal{N}(\mu_{(d\omega/dt)}, \sigma^2_{(d\omega/dt)})$$

This produces trajectories that qualitatively resemble actual keratocyte migration as well as a realistic distribution of angular speed and observed high angular speed autocorrelation functions seen in some cells [7]; however, it cannot generate bimodal angular speed distributions.

II. Computational model of asymmetric centripetal-flow induced keratocyte turning

A. Myosin-powered retrograde actin network flow

Experimental and theoretical studies have established that myosin II (hereafter referred to as "myosin") contracts actin arrays and generates contractile stress, and that this stress grows with increasing myosin concentration [8, 9]. We make the simplest assumption that the myosin-generated contractile stress, kM, is linearly proportional to the myosin density, M. Here k is the proportionality coefficient (typical force per myosin unit) that in the model depends on blebbistatin/calyculin A treatment. The contractile force applied to the actin network is the divergence of the stress; in the case of the scalar stress, its gradient, $k\nabla M$. Following Rubinstein et al. 2009 [10], we assume that adhesion complexes generate viscous resistance to the flow of F-actin relative to the substrate (with velocity $\vec{U}$ in the lab coordinate system). The respective resistance force, $\zeta\vec{U}$, where ζ is the effective drag coefficient that we also refer to as adhesion strength, is balanced by the active contractile stress: $\zeta\vec{U} = k\nabla M$.

The simple equation, $\zeta\vec{U} = k\nabla M$, does not take into account passive stresses in the F-actin network due to its deformation during the flow. To add these passive stresses, we follow Rubinstein et al. 2009 [10] and assume that these stresses have a viscous character with a relevant time scale of tens of seconds. The small elastic component of the stress in the lamellipodium can be neglected [10], so we model a combination of the shear and deformation stresses in the F-actin with the formula $(\frac{1}{3}\mu + \mu_b)(\nabla \cdot \vec{U})I + \mu(\nabla\vec{U} + (\nabla\vec{U})^T)$, where μ and μ_b are the shear and bulk viscosities, respectively, and I is the identity tensor. Adding the divergence of these passive stresses to the myosin and adhesion forces results in the force balance equation determining the flow rate of F-actin:

$$\left[\left(\frac{1}{3}\mu + \mu_b\right)\nabla\nabla\cdot\vec{U} + \mu\nabla^2\vec{U}\right] + k\nabla M = \zeta\vec{U} \tag{1}$$

Using a zero pressure boundary condition at the free lamellipodial boundary:

$$\vec{n} \cdot \left[\left(\frac{1}{3}\mu + \mu_b \right) (\nabla \cdot \vec{U}) I + \mu \nabla \vec{U} + (\nabla \vec{U})^T) + kM \right] = 0 \tag{2}$$

Here $\vec{n}$ is the local normal unit vector to the lamellipodial boundary. This model simplifies the analysis by assuming that the F-actin viscosity is spatially constant and independent of the F-actin density. Note that due to this assumption we do not simulate or track actin density. Including a more detailed assumption of viscosity being a function of the F-actin density does not change the qualitative pattern of the actin flow [10].

B. Myosin transport

Following Rubinstein et al. 2009 [10], we assume that myosin molecules bind and move with the F-actin network. Myosin molecules can detach from the F-actin, diffuse in the cytoplasm and reattach. Here, we assume that detachment and reattachment is rapid, in which case the system of equations for the actin-associated and diffusing myosin molecules [10] reduces to just one equation for the motion of actin-associated myosin [11]. In this model, the rapid cycles of myosin detachment, diffusion in the cytoplasm, and reattachment, effectively result in a slow diffusion of the actin-associated myosin combined with the convective drift of myosin due to coupling with the F-actin that has a characteristic actin network velocity, $\vec{U}$:

$$\frac{\partial M}{\partial t} = D_M \nabla^2 M - \nabla \cdot \left(\left(\vec{U} - \nabla H(\vec{x} - \vec{x}_{cm}) \right) M \right), \tag{3}$$

where D_M is an effective diffusion constant. The second term in Eq. (3) has an additional factor to account for the observed expulsion of myosin from the center of the cell, $\vec{x}_{cm}$, where the nucleus is located. Computationally this expulsion is achieved by introducing the smoothed Heaviside function:

$$H(\vec{x} - \vec{x}_{cm}) = \frac{f_0 \exp^{-|\vec{x} - \vec{x}_{cm}|^2 / r_n^2}}{1 + |\vec{x} - \vec{x}_{cm}|^4 / r_n^4} \tag{4}$$

where r_n is the effective radius of the nucleus and f_0 is the effective repulsion strength. This function is approximately equal to f_0 in the area covered by the nucleus and zero outside the nucleus. The gradient of this function introduces effective drift of myosin away from the nuclear center at the nuclear boundary.

The boundary conditions for the myosin transport are:

$$-\vec{n}\cdot\left[D_M\nabla M - M\left(\vec{U}-\nabla H(\vec{x}-\vec{x_0})\right)\right] = V_\perp M, \quad V_\perp < 0 \tag{5}$$

$$M = 0, \quad V_\perp > 0 \tag{6}$$

where $\vec{n}$ is the outward normal at the cell boundary. The left hand side of Eq. (5) is the total (diffusion-drift) flux of myosin at the retracting boundary. When the boundary is not moving ($V_\perp = 0$), Eq. (5) becomes the usual boundary condition with no flux. When the boundary is moving inward ($V_\perp < 0$), additional inward myosin flux arises due to the fact that the total myosin is conserved, so the inward-moving cell edge collects myosin at the edge (with local density M) and advects this myosin into the cell interior. To conserve the myosin density, this advection flux is the expression in the right hand side of Eq. (5). In addition, Eq. (6) describes the approximate no flux condition at the protruding boundary ($V_\perp > 0$). Due to effective diffusion, we have to use the total (diffusion-drift) flux of myosin at the protruding boundary. However, the effective diffusion is very slow. Thus, we can use the approximation that the drift of myosin flux at the protruding boundary is equal to zero, which means $M = 0$ at this part of the boundary (Eq. 6), which matches experimental measurements (**Figure 4A**). This approximate boundary condition, where we treat the minuscule myosin concentration at the protruding edge as zero, does produce a very small loss of conservation of total myosin density (typically $< 0.02\%$ of myosin per second is lost), so to restore the conservation of total myosin density we have added an additional step of uniformly re-normalizing the myosin density to each time step. This procedure amounts to assuming that there is a reservoir of unbound myosin that is in equilibrium with the bound pool.

C. Mobile cell boundary

The cell boundary evolves according to the superposition of the inward boundary displacement from myosin-induced contraction and the outward displacement from actin polymerization. The net rate of boundary displacement, $V_\perp$, in the locally normal direction is expressed in the model as

$$V_\perp(s) = \vec{U}(s)\cdot\vec{n}(s) + \left[V_p - \frac{2\tau_0}{R(s)}\right] \tag{7}$$

where s is the arclength parameter marking the position along the cell boundary, $\vec{n}(s)$ is the outward pointing locally normal vector and $\vec{U}(s)\cdot\vec{n}(s)$ is the local actin centripetal flow given by Eq. (1) projected onto the normal

of the boundary. The term in the square brackets is the net actin polymerization rate, where V_p is the polymerization rate, and the second term accounts for the effect of the membrane tension on decreasing the polymerization rate. Experimentally, it has been established that lamellipodial area is conserved, likely due to a fixed amount of plasma membrane area [11]. As the membrane is effectively unstretchable, the membrane tension would increase as the cell area increases, decreasing the polymerization rate. We model these mechanics by assuming that V_p is constant along the boundary but decreases when the cell area increases. The second term in the square brackets is the effective Laplace pressure, which prevents development of sharp corners at the boundary. This term is small and does not affect the global cell behavior, and scales with the local boundary curvature $1/R(s) = -\vec{n}(s) \cdot \partial_s \vec{n}(s)$. The proportionality coefficient, τ_0, is defined by: $\tau_0 = \sigma_0 l_0^2/\eta_0$ where σ_0 is the effective membrane tension (along the boundary), l_0 is a length scale of molecular dimension and η_0 is the effective drag coefficient for the membrane as the surface evolves. In essence, $2\sigma_0/R$, is the Laplace pressure, multiplied by l_0^2 to give us the total force on a patch membrane of size l_0^2. If we then divide the total force $2\sigma_0 l_0^2/R$ by the drag coefficient associated with the patch of membrane, then we get the velocity at which the patch of membrane is moving. Note that τ_0 has the same dimension as a diffusion constant.

D. Adhesion

Adhesion strength, ζ, appearing in Eq. (1) varies spatially [10] so $\zeta = \zeta(\vec{x})$. We model function $\zeta(\vec{x})$ using patterns based on experimentally measured traction forces and distributions of adhesion molecules [10]. It is known that the traction force is weakest at the rear and strongest at the sides of cell [12]. This implies that adhesion strength should be the greatest at the sides and the smallest at the rear, and the strength of adhesion at the leading edge should be in between that of the rear and of the sides (**Figure S3A**).

To come up with a mathematical description for the pattern shown in Figure S3A, it is best to work in the cell frame of reference, and for convenience we use the center of mass $\vec{x}_{cm}$ (center of the cell body in the model) as the origin of our coordinate system. To define the x and y axes, we first compute the eigenvectors of the gyration tensor as defined by $R_{ij} = \int x_i y_i dA$, where the integration is over the whole cell. Because this is a symmetric real tensor, it will diagonalize to create two unique orthogonal eigenvectors $\{\hat{e}_s, \hat{e}_l\}$ as long as the cell is not circularly symmetric. These two eigenvectors, by construction, point along the longest and the shortest dimensions of the cell. We next construct a dynamical vector variable $\hat{N}_{cell}$ which acts

like a compass that follows the shortest dimension ($\hat{e}_s$) corresponding to the rear-front direction. This vector evolves according to:

$$\frac{\partial \hat{N}_{cell}}{\partial t} = -\gamma_n \left(\hat{N}_{cell} - \hat{e}_s \right) \tag{8}$$

where $1/\gamma_n$ is the characteristic fast response time, the exact value of which does not affect the predicted behavior. At the beginning of the run, we set $\hat{N}_{cell}(t=0) = \hat{e}_s(t=0)$ as our initial condition. Since $\hat{N}_{cell}$ points along the short dimension of the cell we may designate it as the y axis and use the perpendicular line crossing $\hat{x}_{cm}$ as the x axis. Using this coordinate system, we initially place two sites of locally maximal adhesion to the sides of the cell where the adhesion strength peaks are at the coordinates $(-h_0, \pm d_0/2)$ (**Figure S3A**). To define the dynamic position of the adhesion peaks at the cell sides, we define a generalized Heaviside step function, keeping in mind that we are using the $\hat{N}_{cell}$ coordinate system:

$$\mathcal{H}(\vec{x}, \vec{x}_0, \vec{a}, \varepsilon) = \frac{1}{2}\left[1 - \tanh\left[\frac{(\vec{x} - \vec{x}_0)((\vec{x} - \vec{x}_0)^T \vec{a}) - 1}{\varepsilon}\right]\right] \tag{9}$$

In this expression, vector quantities should be interpreted as column vectors so that $(\vec{x} - \vec{x}_0)^T$ which stands for the transpose of $(\vec{x} - \vec{x}_0)$ is a row vector. Just like the regular step function, the value of this function is 1 inside some region and 0 outside of this region with a transition zone width approximated by $\varepsilon |\vec{a}|^{-1/2}$. The shape of the region defined by this function is such that if the argument of the tanh function is negative/positive, then position $\vec{x}$ is inside/outside the given region, respectively. To see how this function works, notice that if we multiply out the vectorial quantities in the function argument using $\vec{x} = (x, y)^T, \vec{x}_0 = (x_0, y_0)^T$, and $\vec{a} = (a_x, a_y)^T$, then

$$(\vec{x} - \vec{x_0})((\vec{x} - \vec{x}_0)^T \vec{a}) - 1 = a_x(x - x_0)^2 + a_y(y - y_0)^2 - 1 \tag{10}$$

If we let $a_x = a_y = 1/r^2$, we get

$$(\vec{x} - \vec{x}_0)((\vec{x} - \vec{x}_0)^T \vec{a}) - 1 = \frac{(x - x_0)^2}{r^2} + \frac{(y - y_0)^2}{r^2} - 1 \tag{11}$$

which tells us that the shape of the given region is a circle with radius r centered at $\vec{x}$. If $a_x \neq a_y$, then we have an ellipse. We define ζ with the help of function $\mathcal{H}$ and the coordinate system $\hat{N}_{cell}$ so that it matches closely with the adhesion pattern shown in Figure S3A:

$$\begin{aligned} \zeta(\vec{x}) = \zeta_0 &+ \zeta_l \mathcal{H}\left[\vec{x}, (-d_0/2, -h_0)^T, (1/r_0^2, 1/r_0^2)^T, \varepsilon\right] \\ &+ \zeta_r \mathcal{H}\left[\vec{x}, (d_0/2, -h_0)^T, (1/r_0^2, 1/r_0^2)^T, \varepsilon\right] \\ &+ \zeta_f \left(1 - \mathcal{H}\left[\vec{x}, (0, 0, -h_2)^T, (4/d_1^2, 1/h_1^2)^T, \varepsilon\right]\right) \end{aligned} \tag{12}$$

Here ζ_0 is the baseline value for the adhesion strength (light blue region at the rear shown in Figure S3A), ζ_f is the adhesion strength value at the leading edge, and ζ_l and ζ_r are the adhesion strength values at the left and right sides of the cell respectively.

E. Varying adhesion strengths ζ_l and ζ_r in time

To test how adhesion asymmetry causes the cell to turn dynamically, we allow the adhesion strengths at the sides, ζ_l and ζ_r, to oscillate in time according to equations:

$$\zeta_l = \zeta_1^0 + \Delta\zeta_w \sin(2\pi\nu t) \tag{13}$$

$$\zeta_r = \zeta_r^0 - \Delta\zeta_w \sin(2\pi\nu t) \tag{14}$$

where ζ_l^0 and ζ_r^0 are the baseline adhesion strengths at the two sides. $\Delta\zeta$ is the maximum deviation from ζ_w and $1/\nu$ is the period of oscillation of adhesion strength. We also used other functions of time (that are always bounded from below and above) to model more stochastic variance of the adhesion strengths. For example, we used Ornstein-Uhlenbeck stochastic process (random walk in time of an overdamped harmonic oscillator perturbed by the white Gaussian noise). Results did not depend strongly on the nature of the time-dependent variation.

F. Adhesion dynamics and boundary-crossing simulation

We modeled cells crossing boundaries of different adhesion strength, by first taking $\zeta^{high}(\vec{x})$ and $\zeta^{low}(\vec{x})$ to denote the adhesion strength of the cell when the cell is crawling on substrates with high and low adhesivity (as measured by the RGD density) respectively. To smoothly let the cell cross between the two different substrates and thus transition between ζ^{high} and ζ^{low} (and reverse), we again use a different type of Heaviside step function Λ which gives a value of one to the region in space with high adhesion and a value of zero to the areas with low adhesion substrate. Mathematically, this may be expressed as (using the lab coordinate system)

$$\zeta(\vec{x}) = \zeta^{low}[1 - \Lambda(\vec{x})] + \zeta^{high}\Lambda(\vec{x}) \tag{15}$$

The precise form of Λ is similar to that for $\mathcal{H}$ (Eq. 9) with a different argument function.

G. Simulation setup

The initial condition for our simulation was a circular cell of area $A = 600\mu\text{m}^2$. We initially spread myosin uniformly over the whole cell. Symmetry was then broken by choosing a fixed orientation of the short axis of the cell, $\hat{N}_{cell}$, and biasing adhesion strength to be asymmetric across the long axis of the cell during the first minute, of the simulation. During this first minute cells typically evolved into the characteristic crescent shape, after which $\hat{N}_{cell}$ was allowed to evolve according to Eq. (8).

All calculations are carried out using LGPL-licensed finite-element solver FreeFem++ (www.freefem.org) as described in detail in [11].

H. Model parameters

The model variables and parameters are listed in the Tables S1 to S4 below. Most of the parameter values are taken directly from our previous publications [10, 11] with minor changes. In the following sections we discuss the physically relevant parameters.

Table 1: Model Variables

Variable	Meaning	Dimension
t	time	s
s	arc length	μm
$\vec{x}$	two-dimensional coordinate	μm
$M(\vec{x},t)$	myosin concentration	units/μm^3
$\vec{U}(\vec{x})$	local F-actin flow velocity	μm/s
$\vec{n}(\vec{x})$	local normal unit vector to the lamellipodial edge	non-dimensional
$\zeta(\vec{x},t)$	adhesion strength/drag-coefficient	$nN \cdot s/\mu\text{m}^4$
$V_\perp(s)$	net local protrusion/retraction rate	μm/s
V_p	local polymerization rate	μm/s
$R(s)$	local radius of curvature	μm

I. Viscous actin-myosin network

We take the characteristic length to be the typical cell size (from front to back) $L_0 = 10\mu$m and the characteristic speed to be the characteristic cell speed, $V_0 = 0.2\mu$m/s which is comparable to the retrograde flow rate of the actin network. We set the shear viscosity, $\mu = 5$ kPa$\times$s [10]. Given that the bulk viscosity is normally higher than the shear viscosity (as the gels are

Table 2: Definition of adhesion strength related parameters

Parameter	Meaning	Dimension
ζ_0	baseline adhesion strength	nN·s/μm^4
ζ_l	adhesion strength coefficient for the left wing	nN·s/μm^4
ζ_r	adhesion strength coefficient for the right wing	nN·s/μm^4
ζ_f	adhesion strength coefficient for the leading edge (front)	nN·s/μm^4
ζ_l^0	baseline adhesion strength for the left wing	nN·s/μm^4
ζ_r^0	baseline adhesion strength for the right wing	nN·s/μm^4
$\Delta\zeta$	maximum amplitude of adhesion strength perturbation	nN·s/μm^4
ν	frequency of modulating adhesion strength	s$^-$1
h_0	y-displacement relative to the cell center for the side adhesion patches	μm
h_1	front-back length	μm
d_o	x-displacement relative to the cell center for the side adhesion patches	μm
h_1	width parameter for front adhesion patch size	μm
r_0	side adhesion patch size	μm
ε	adhesion transition zone width parameter	dimensionless

more resistant to compression than shear) we use the value $\mu_b = 100$ kPa×s as the bulk viscosity [10]. In order for the myosin stress to generate the observed flow of the order of $V_0 = 0.2$ μm/s inside a lamellipodium with characteristic thickness of $h = 0.2$ μm, the typical force scale is $\mu h V_0 = f_0 = 200$ pN: In our calculations, we multiply the viscosities by the characteristic thickness of the lamellipodium $h = 0.2$ μm in order to convert the 3D stress derivatives into the 2D surface force densities. To non-dimensionalize Eq. (1), we choose $k = \mu V_0 L_0^2 = 100$ nN×μm based on dimensional analysis. Using this coefficient k, 100 units of mysoin in our scheme are expected to generate an average force density on the order of $100k/L_0^4$ and hence are capable of generating an average traction force on the order of $100kh/L_0^4 \sim 200$ Pa, comparable to known traction force data [13, 14]. For all our simulation runs, unless stated otherwise, we use the total amount of myosin $M_{total} = 80$ non-dimensional units. (Note that M_{total} is conserved in the model.) We set the diffusion coefficient $D_M = 1.2\mu$m^2/s to be sufficiently small to keep the dimensionless Péclet number $Pe = \frac{kM}{\zeta_0 D_M} \gg 1$ such that the actin flow dominates over diffusion [15] when the adhesion strength is minimal ($\zeta = \zeta_0$) [11, 16].

J. Myosin dynamics with fixed cell boundary

As part of our test calculations, we consider what happens when the shape of the cell is fixed ($V_\perp = 0$), but the cell is turning. To simulate such a situation, we solve Eq. (3) while taking the motion of the turning cell explicitly into account. This is done by adding a kinematic flow to Eq. (3) so that it becomes:

$$\frac{\partial M}{\partial t} = D_M \nabla^2 M - \nabla \cdot \left(\left(\vec{U} + \vec{U}_{kinematic} - \nabla \mathcal{H}(\vec{x} - \vec{x}_{cm}) \right) M \right) \qquad (16)$$

$$\vec{U}_{kinematic} = -\Omega\hat{z} \times (\vec{x} - \vec{x}_\omega)$$

Here $\vec{x}_\omega$ is the center of pivoting motion and $-\Omega\hat{z}$ is the angular velocity of the cell. The negative sign accounts for the fact that myosin should drift in the direction opposite to the cell motion. $\hat{z}$ is the unit vector pointing out of the surface on which the cell crawls. For these computational runs, we choose $\vec{x}_\omega = (40\mu\text{m}, -5\mu\text{m})$ relative to the cell center-of-mass and $\Omega = 1/250$ s^{-1}. These values indicate that the cell is moving at a linear speed of $\bar{V} = \Omega|\vec{x}_\omega| = 0.2$ μm/s and angular speed of about $\bar{V}/(2\pi|\vec{x}_\omega|) \times 360\,\text{deg} = 0.23$ deg/s, both comparable to measured speeds and angular speeds from the experimental work.

K. Magnitude of adhesion strength

The strength of adhesion is characterized by the coefficients introduced in Eq. (12), namely $\{\zeta_0, \zeta_l, \zeta_r, \zeta_f\}$. We fix the baseline strength at $\zeta_0 = 0.03$ nN s/μm^4 for all of our runs. This value is comparable to the low adhesion strength we previously reported in [11]. The value for the other coefficients varies depending on what system we are studying but we try to keep them all comparable to the 'medium' values that we have reported previously $\bar{\zeta} = 0.4$ nN$\times$s/μm^4[11]. Note that with the 'medium' values of adhesion strength and with a characteristic retrograde flow rate in our simulation of $\bar{U} = 0.2$ μm/s, the characteristic traction force will be $\bar{\zeta}\bar{U}h \sim 16$ Pa, which is comparable to the experimentally measured traction force (5-10 Pa).

L. The nucleus

In our two-dimensional model the nucleus is represented as a disc with radius $r_n = 7.5$ μm centered at the cell center-of-mass $\vec{x}_{cm}$. To effectively repel both myosin and adhesion from the region where the nucleus resides, we need to choose $f_o \exp(1)/r_n = |\nabla\mathcal{H}|_{|\vec{x}-\vec{x}_0|=r_n} > V_0$ for the repulsion to be strong enough to counteract the actin flow. We choose $f_0 = 1$ μm^2/s, which yields $f_0 exp(1)/r_n = 0.35$ μm/s.

M. Cell shape dynamics

The dynamics of the cell boundary are dictated by the balance of the net local protrusion/retraction rate and the Laplace pressure. The strength of the Laplace pressure term is governed by $\tau_0 = \sigma_0 l_0^2/\eta_0$. We chose the tension σ_0 to be 0.1 nN/μm [17]. The drag coefficient for the membrane η_0 scales, according to Stoke's Law, as $\approx 6\pi\mu_0 l_0$, where $\mu_0 = 1$ cP is the viscosity of water. As for l_0, it should be the size of a lipid molecule, approximately 1 nm. Using these numbers, $\tau_0 = 0.5$ μm^2/s. In this study, we used a comparable

value of $\tau_0 = 0.1$ μm^2/s, which means that the tension is slightly less than 0.1 nN/μm.

N. Dependence of the model behavior on the parameters

The most important parameters in the model are the myosin strength k, the adhesion strength ζ, the actin viscosity μ, and the characteristic cell speed V_0. The model behavior is sensitive to these parameters in the sense that for the shape and movement of the model cell to resemble the real cell, there is a number of constraints on these parameters that have to be in place, analyzed in detail in [10, 11]. These constraints are not rigid: a few-fold changes of these parameter values (Table 3) still predicts qualitatively all the observed behavior. Similarly, the model is robust to a few fold change of all characteristic adhesion strengths used (Table 4). The model is even less sensitive to all other parameters listed in Table 3: changes of up to an order of magnitude of their values (one at a time, of course) do not change the predicted behavior qualitatively. We emphasize that most of the parameters orders of magnitude are known from extensive studies of keratocyte cells.

Table 3: Non-adhesion related constant model parameters

Parameter	Meaning	Dimension
V_0	characteristic cell speed	0.2 μm/s
L_0	characteristic radius	10 μm
h	cell thickness	0.2 μm
A	cell area	600 μm^2
M_{total}	total myosin	80 units
D_M	effective myosin diffusion constant	1.2 μm^2/s
μ	shear F-actin viscosity	5 kPa·s
μ_b	bulk F-actin viscosity	100 kPa·s
k	myosin force parameter	100 nNμm^2/s
f_0	nucleus repulsion strength	1 μm^2/s
r_n	nucleus radius	7.5 μm
τ_0	membrane tension parameter	0.3 μm^2/s
γ_n	decay constant for the director $\hat{N}_{cell}$	1/5 s^{-1}

Table 4: The values of adhesion strength parameters used

Parameter [Dim]	Standard	High Adh. Sub.	Low Adh. Sub.	Mild Turn	Tight Turn
ζ_0 [nN·s/μm^4]	0.03	0.03	0.03	0.03	0.03
ζ_f [nN·s/μm^4]	0.4	0.4	0.12	0.4	0.4
ζ_l [nN·s/μm^4]	0.5	0.5	0.15	N/A	N/A
ζ_r [nN·s/μm^4]	0.5	0.5	0.15	N/A	N/A
ζ_l^0 [nN·s/μm^4]	N/A	N/A	N/A	0.5	0.5
ζ_r^0 [nN·s/μm^4]	N/A	N/A	N/A	0.5	0.5
$\Delta\zeta$ [nN·s/μm^4]	N/A	N/A	N/A	0.1	0.45
ν [s$^-$1]	N/A	N/A	N/A	0.5	0.5
h_0 [μm]	2	2	2	2	2
h_1 [μm]	13	13	13	13	13
d_0 [μm]	14	14	14	14	14
d_1 [μm]	22	22	22	22	22
r_0 [μm]	2.5	2.5	2.5	2.5	2.5
ε [dimensionless]	.25	.25	.25	.25	.25

III. Simulation results

A. Asymmetries in myosin distribution, actin flow and traction forces in turning cells

We first considered a cell with a fixed shape, chosen to approximate an experimentally measured turning cell shape. Similar to most observed turning cells, there is a lower aspect ratio on the slower side and a higher aspect ratio on the faster side, i.e. the outer wing is more elongated than the inner wing. For simplicity, in these simulations we removed the nucleus and its effects from the cell center. With the fixed cell boundary, we used the kinematic actin-myosin flow of a turning cell as explained above in Eq. (16), as well as a fixed adhesion distribution in time. We tested two distributions of adhesions to see which could replicate observed measurements of actin flow, myosin distribution and traction forces. In one simulation, adhesion was constant in space, while in the other it varied in space with adhesion higher on the inner side of the turning cell. The adhesion distribution with resulting simulation results are presented in Figure S3. We observed that the myosin distribution in both cases was biased toward the fast side of the cell due to the kinematic actin flow, with only slight insignificant differences in myosin distributions between these two cases. However, as presented in the main text, only an asymmetric adhesion distribution could replicate experimental measurements of traction forces.

B. Boundary crossing and myosin asymmetry

We used the free-boundary model of the cell to simulate the cell movement while crossing a boundary between high and low adhesions, as described above. In the simulations at each time step, we scaled the adhesion

strength pattern depicted in Figure S3A by a factor dependent on the parts of the cell that were on higher or lower adhesion, respectively. The results are shown in Figure 7B and Movie S7a,b. We found that, matching experimental results, cells would turn towards the side of higher adhesion after an asymmetry in adhesion developed at the cell rear.

We also simulated the situation where the density of myosin was increased on one side of the cell (**Movie S6**). The simulation demonstrated that an asymmetry in myosin produces a steady turn away from the side of increased myosin. Yet, once the externally imposed bias in myosin concentration is removed, myosin re-distributes around the cell, the cytoskeletal symmetry is restored, and the cell starts to move straight. This matched experimental findings from asymmetric exposure to the myosin activating small molecule calyculin (**Figure 6A**). Thus the combined experimental and simulation results indicate that the positive feedback between the kinematics of turning and myosin distribution are sufficient for transient but not persistent turning. Conversely, asymmetry in protrusion was insufficient to produce cell turning (**Movie S8**).

C. Turning behavior with myosin-adhesion feedback

As the computations with the free-boundary model were computationally expensive, we developed the following combined analytic-computational theory to examine long time scale cell trajectories. We first fixed the difference $\Delta\zeta$ between the left and right adhesion strengths. As a result, the cell, after a brief transient relaxation, started to move with steady shape and angular speed, ω, along a trajectory with constant radius of curvature, R. Also as a result, a steady difference in myosin concentration, ΔM, between the left and right parts of the cell developed. We repeated such simulations varying the value of $\Delta\zeta$ from 0 to the maximum (no adhesion at one side), and measured ΔM, ω, and R for each adhesion asymmetry (**Figure S4A-C**). We found a strong relationship between the asymmetry in adhesion and the predicted rate of turning and myosin asymmetry. In comparison, when we varied the adhesion strength at the leading edge, we found that such variance did not affect cell turning behavior significantly (**Figure S4A,B**).

We found that the angular speed is an approximately linear function of the left-right adhesion difference: $\omega \approx \alpha\Delta\zeta$, and the myosin concentration difference between the left and right sides of the cell is an approximately linear function of the angular speed: $\Delta M \approx \beta\omega$ (**Figure S4A-C**). Here α and β are defined as constant parameters identified in the simulations.

We then followed the experimental and theoretical findings in [18] of the negative feedback between local contraction and adhesion strength. In [18],

the adhesion strength was the function of the local actin flow rate, but as the flow rate V is proportional to the ratio of the myosin concentration to the adhesion strength, here for simplicity we assume that the adhesion strength is the following function of the myosin concentration: $\zeta = \zeta_1 + (\zeta_0 - \zeta_1)(0.5 - arctan(s(m - \bar{m}))/\pi)$, so that the adhesion strength is a decreasing function of the myosin concentration m (**Figure S4D**). This is also consistent with the observed and predicted biphasic relationship between actin retrograde flow speed and traction stress [19], and the hypothetical "molecular-clutch" model of adhesions [20]. At the inner rear of the turning keratocyte, inward actin flow is slow and the molecular clutch of adhesions is in place, creating large traction forces. At the outer rear of the turning keratocyte, inward actin flow is high secondary to myosin contractility and the molecular clutch of adhesions fails, leading to small traction forces. To appropriately model our data, it is important that the adhesion strength decreases slowly at low myosin densities, faster at moderate myosin densities and slower again at high myosin densities, as in **Figure S4D**. However, the exact functional form of this dependence is not critical, and we also note that such functional dependencies are ubiquitous in biology [21]. In the $\zeta(m)$ relation, ζ_0 is the high adhesion strength (Table 4), and $\zeta_1 = \zeta_0/2$ is the low adhesion strength, $s = 20$ is the parameter determining how fast the adhesion drops at threshold myosin density $\bar{m}$ [18]; we choose $\bar{m} = 1.2$ where $M = 1$ corresponds to average myosin density at the cell rear in the state of the straight movement.

According to this assumption of negative feedback of myosin contractility on adhesion strength, if the cell moves with angular speed ω, then there will be the resulting difference in myosin concentrations at the cell left and right sides, $M+m$ and $M-m$; $2m \approx \beta\omega$. Then, there will be the following side-to-side difference in the centripetal flow: $V_l \sim (M+m)/\zeta_l, V_r \sim (M-m)/\zeta_r$, where $\zeta_l == \zeta_1 + (\zeta_0 - \zeta_1)(0.5 - arctan(s(M + m - \bar{m}))/\pi)$, and $\zeta_r == \zeta_1 + (\zeta_0 - \zeta_1)(0.5 - arctan(s(M - m - \bar{m}))/\pi)$. The resulting angular velocity is proportional to the difference $V_l - V_r$, and so:

$$\omega = f(m), f(m) = M\frac{\zeta_l - \zeta_r}{\zeta_l\zeta_r} + m\frac{\zeta_l + \zeta_r}{\zeta_l\zeta_r}, \zeta_{l,r} == \zeta_1 + (\zeta_0 - \zeta_1)(0.5 - arctan(s(M \pm m - \bar{m}))/\pi). \tag{17}$$

On the other hand, we have:

$$\omega \approx \frac{2m}{\beta} \tag{18}$$

The system of Eq. (17,18) is shown graphically in Figure 7C, and the intersections of the two relationships determines the steady turning state of

a cell. We investigate the behavior of this model when the average myosin density (or strength) parameter M – changes. In this figure we can see that for greater myosin strength, there are three steady states, one of which corresponds to straight migration and equal adhesion at the sides ($\omega = 0, \Delta\zeta = 0$), and two others correspond to finite angular speeds and adhesion strength differences at the sides. These two finite angular speeds are the same in magnitude and opposite in sign, and they correspond to rotation in the clockwise and counter-clockwise directions. The movement with $\omega = 0$ is unstable while the two other ones are stable, so a cell with this described negative feedback between local myosin concentration and adhesion strength will switch between turning persistently in two opposite directions, matching the behavior of experimentally observed trajectories (**Figure S1C**). On the other hand, when myosin strength is low, the only stable state corresponds to straight migration and equal adhesion at the sides ($\omega = 0, \Delta\zeta = 0$).

In order to illustrate this point, we numerically solved the system of two dynamic equations:

$$\frac{d\omega}{dt} = \frac{1}{\tau_\omega}(f(m) - \omega), \frac{dm}{dt} = \frac{1}{\tau_m}(\beta\omega/2m) + B(t) \tag{19}$$

for the angular speed and myosin difference that produce the steady solutions given by Eq. 17 and 18, and describe the relaxation of the angular speed and myosin difference to their steady states values with characteristic times of τ_ω, and τ_m respectively. In the second equation of Eq. 19, the term $B(t)$ is used to describe stochastic uncorrelated noise. Numerically, we can solve Eq. 19 using the Forward Euler method as follows:

$$\begin{aligned} \omega(t + \Delta t) &= \omega(t) + \frac{\Delta t}{\tau_\omega}(f(m(t)) - \omega(t)), m(t + \Delta t) \\ &= m(t) + \frac{\Delta t}{\tau_\zeta}(\beta\omega(t)/2 - m(t)) + (2D\Delta t)^{1/2} Z \end{aligned} \tag{20}$$

Here the stochastic term D is the effective diffusion of adhesion (random steps of adhesion change), and Z is the standard normal random variable. Note, that the same results can be achieved if the angular speed is noisy, or both speed and adhesion are noisy, with the magnitude of the noise adjusted to fit the results.

We simulated Eq. 20 numerically using the parameters $\bar{M} = 1.1$ for control value of the myosin strength and, $\bar{M} = 0.8$ for low value of the myosin strength, $D = 0.01, \beta = 0.45$ (other parameters are listed above) and recorded the time series of cell angular speed. When the parameter $M <$

0.9, the negative feedback of myosin on adhesion is too weak and the only stable steady state corresponds to straight motion. When the parameter $M > 1$, the negative myosin-adhesion feedback is strong enough to provide the bistable cell switching behavior that results in peaks in the angular speed distribution, which correspond to persistent turning with rates on the order of ~ 1 degree per second, as observed (**Figure 6D**). Simulations give distributions of angular speeds, autocorrelation functions and trajectories illustrated in Figure 6E, which agrees with our experimental measurements.

In addition, this model reproduces the experiment with motion in the electric field as follows. We observe that the electric field tends to orient the leading edge of the cell in the direction of the cathode. We model this tendency by adding the term $-r\theta$ to the equation for the rate of change of the angular velocity, where θ is the angle at which the cell moves relative to the cathode direction. Essentially, the angular velocity of the cell rear is slowed down by the leading edge pull proportionally to the deviation from the cathode direction when the cell is turning away from this direction, and accelerated when the cell is approaching this direction. Respective system of equation is:

$$\frac{d\omega}{dt} = \frac{1}{\tau_\omega}(f(m) - \omega) - r\theta, \tag{21}$$

$$\frac{dm}{dt} = \frac{1}{\tau_m}(\beta\omega/2m) + B(t), \tag{22}$$

$$\frac{d\theta}{dt} = \omega. \tag{23}$$

Numerical solutions of these equations with $r = 0.3$ and all other parameters the same as above are shown in (**Figure S4**) for both weak ($M = 0.8$) and strong ($M = 1$) myosin contractility.

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