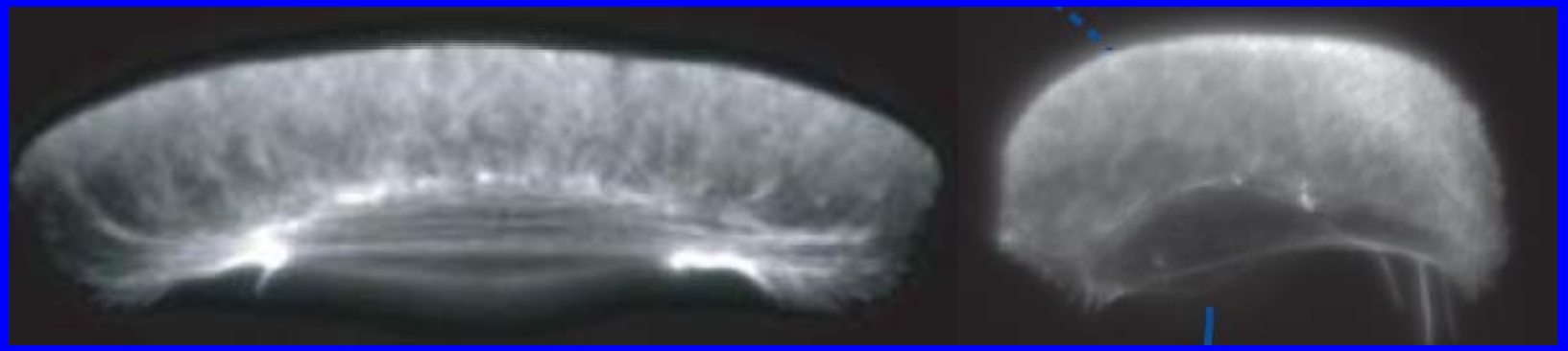
Neurobiology & Mathematics

University of California at Davis

Mechanical Strategies for Cell Crawling

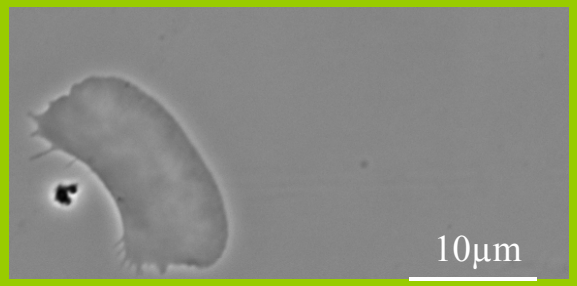
Alex Mogilner



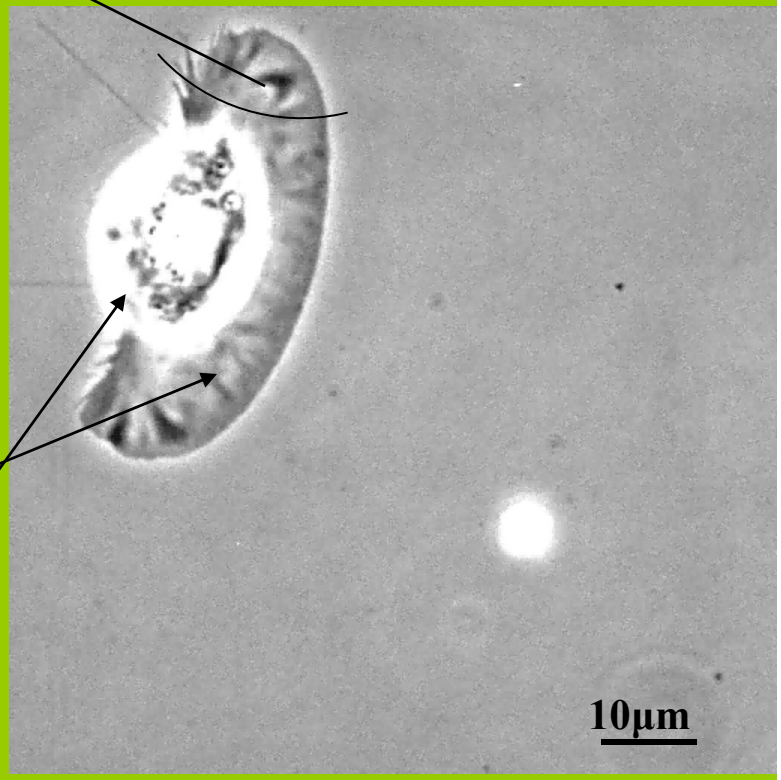
Images: Allen, Theriot et al

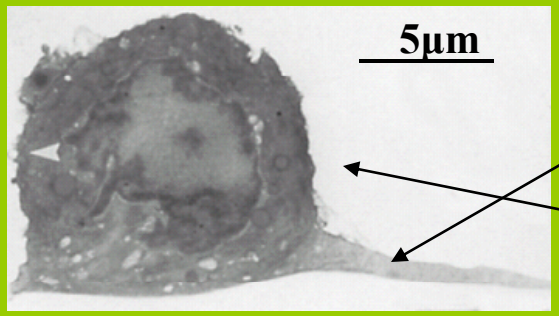
Banff, August 2011

Model system: **fish epithelial keratocytes**



fragments move like the whole cell





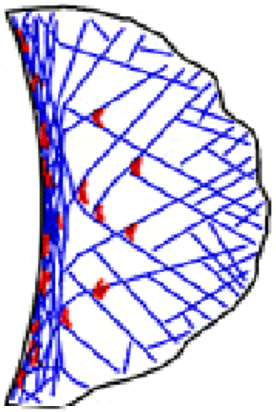
lamellipodium

cell body

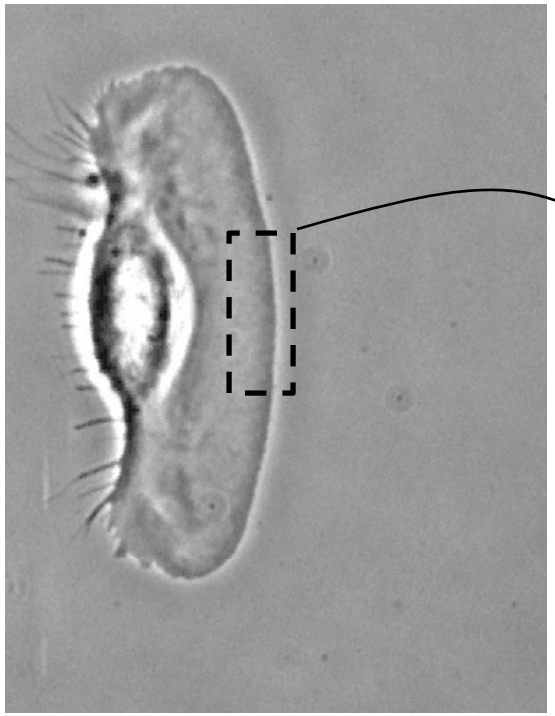
Anderson, K., et al. (1996) *J. Cell Biol.* **134**: 1209-1218

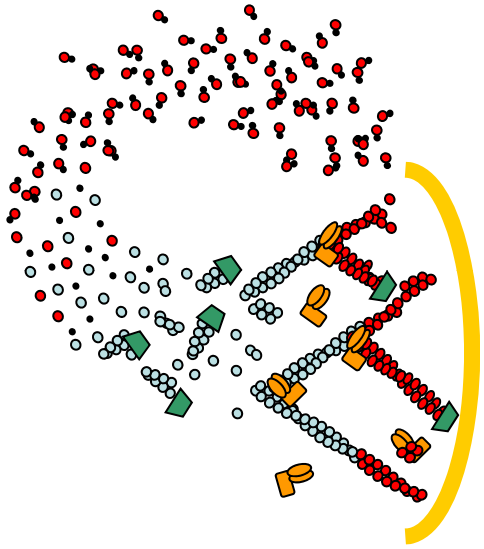
- **Persistent motion**: nearly constant shape, steady state motility
- **Rapid crawling**: 0.1 - 0.5 **µm/s; no microtubules needed**
- **Flat lamellipodium**: 2D molecular machine (good for microscopy and modeling)

Lamellipodial molecular machinery: treadmilling of actin-myosin network



Svitkina, Verkhovsky, Borisy,





Mullins, Pollard

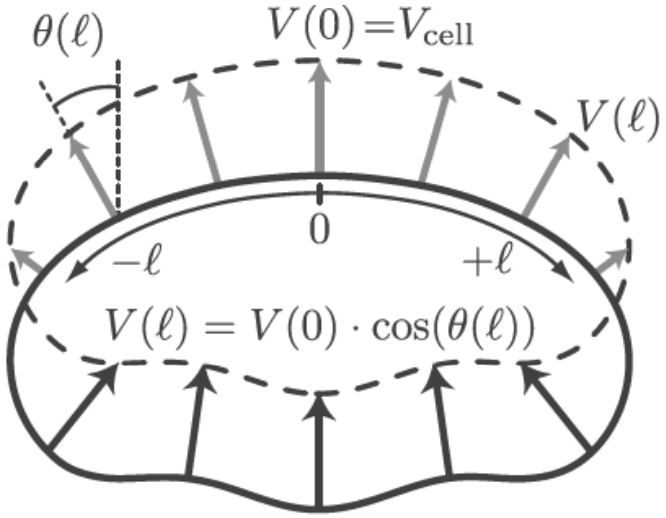
How does this actin-myosin array self-organize?
How is the front protruding?
Rear retracting?
What keeps the sides stable?

Dynamic cell geometry:

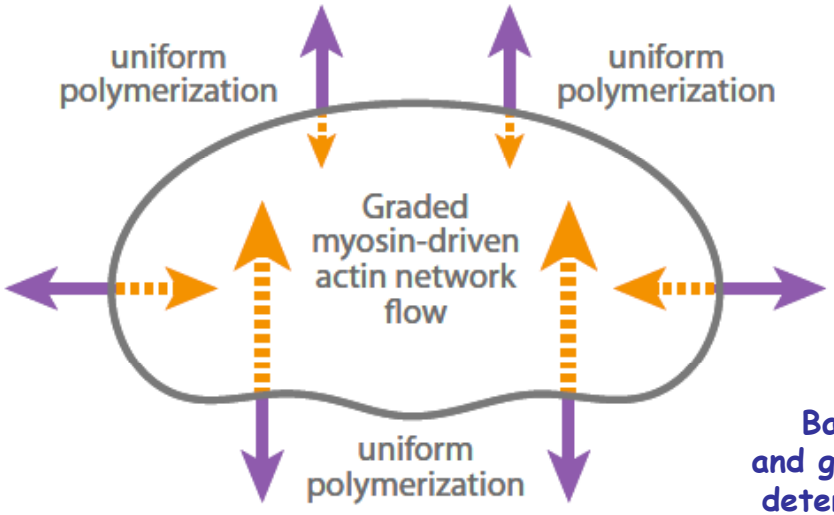
Lee, Theriot, Jacobson et al 1993

Graded Radial Extension model:

balance of (spatially graded) extension and contraction determines cell shape

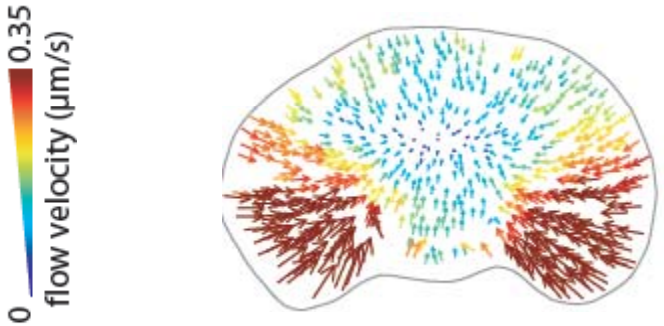


But what are the mechanisms?



Balance of uniform F-actin growth and graded myosin-powered F-actin flow determines the cell shape and movement

Barnhard et al, PLoS Biology, 9(5): e1001059 (2011)

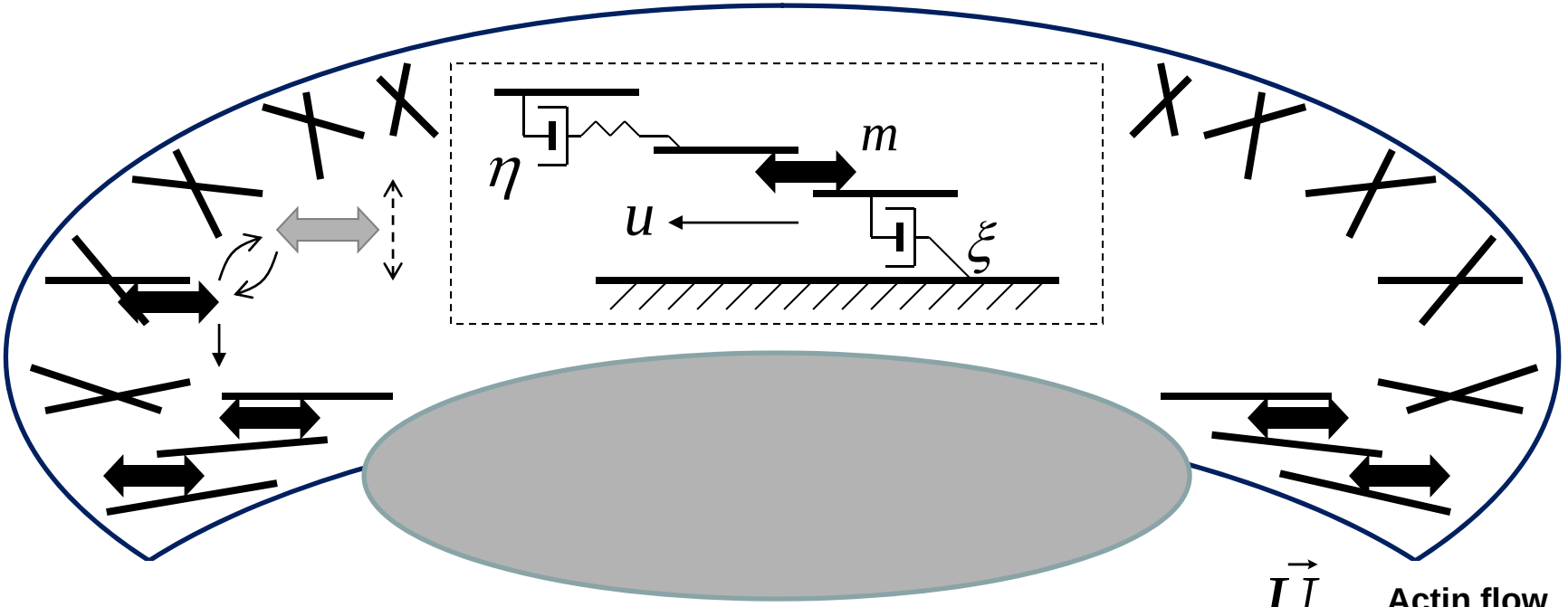


myosin

The centripetal actin flow is indeed graded, and myosin is biased to the rear, but why?

Mechanical model of contractile viscous actin gel

Barnhard et al, PLoS Biology,2011
(based on earlier model in BJ 2009)



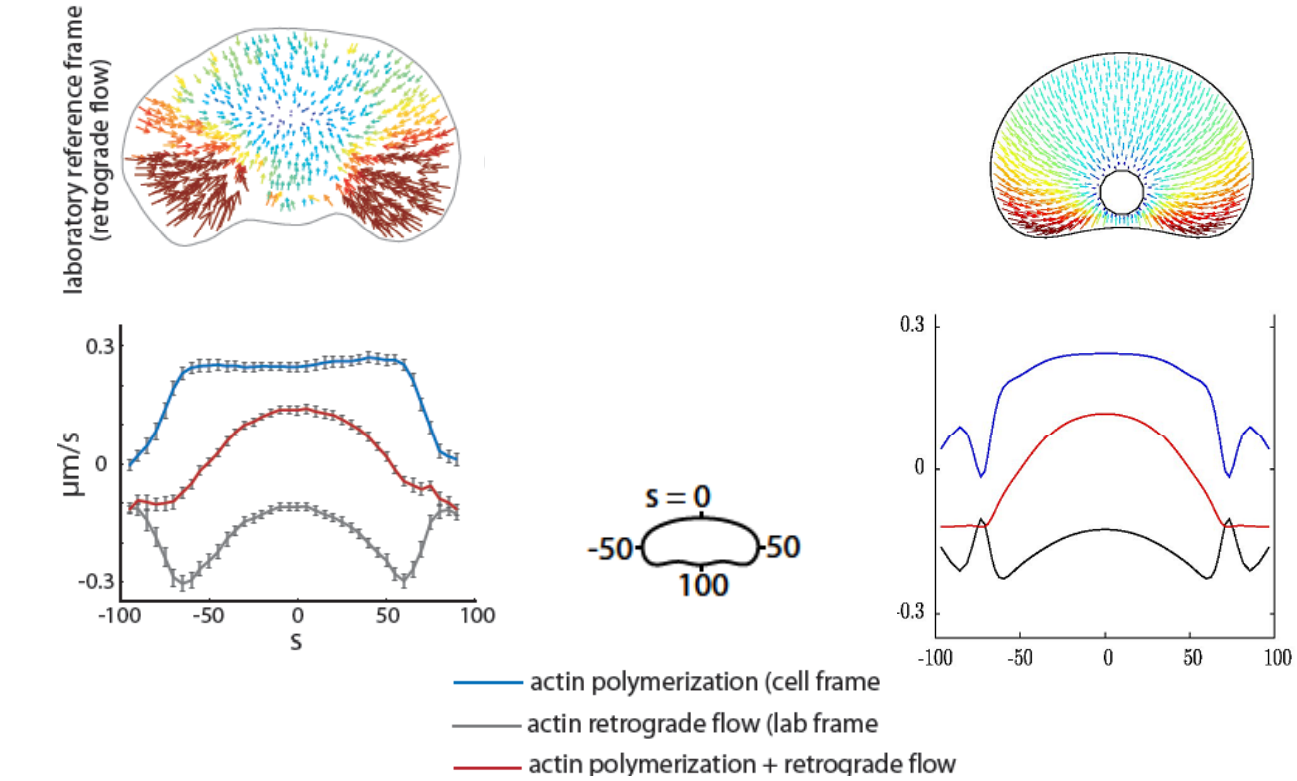
$$\left[\left(\frac{1}{3}\mu + \mu_b\right)\nabla\nabla\cdot\vec{U} + \mu\nabla^2\vec{U}\right] + k\nabla M = \zeta\vec{U}$$

$$\frac{\partial M}{\partial t} = D_M\nabla^2 M - \nabla\cdot((\vec{U} - \vec{V_{cell}})M)$$

$\vec{U}$	Actin flow
M	Myosin density
μ	Actin viscosity
k	Contract stress
ζ	Adh strength
D_M	Myosin diffusion
$\vec{V}_{cell}$	Cell velocity

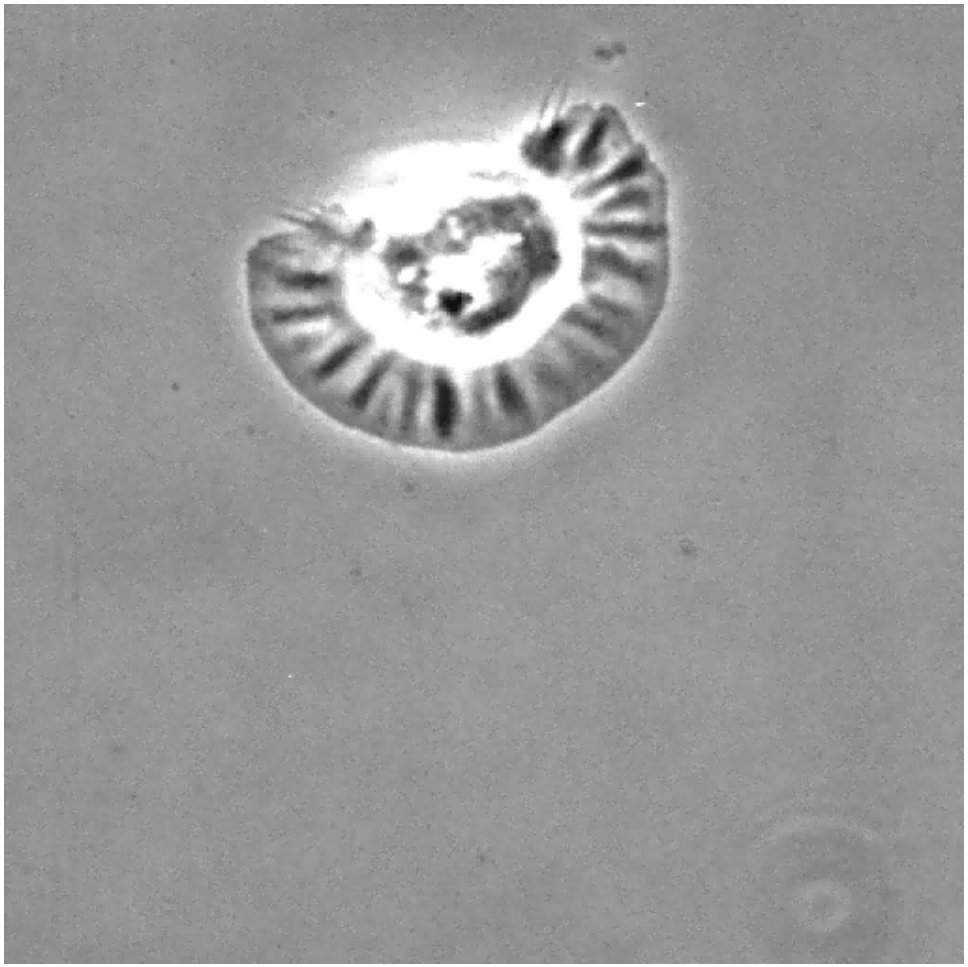
…can explain the graded myosin-powered centripetal actin flow…

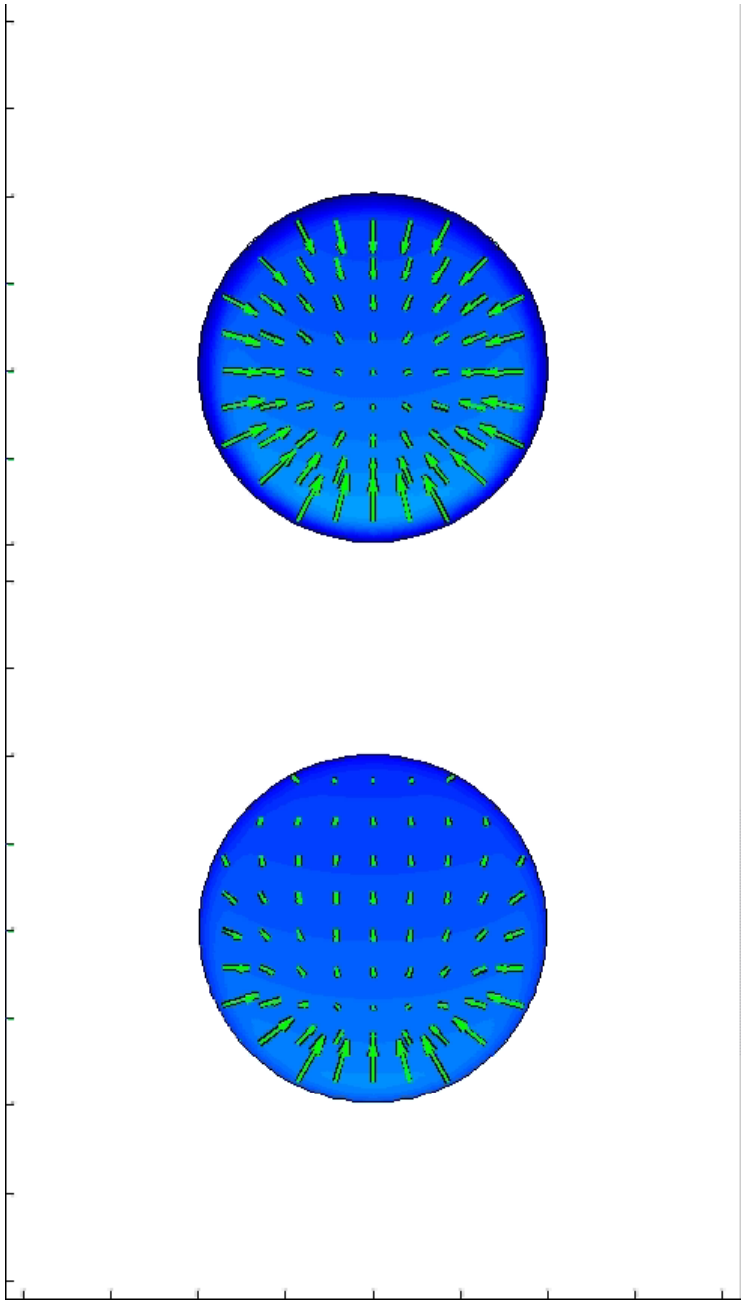
Barnhard et al, PLoS Biology, 2011



…but the cell shape and movement are not that easy:

Wolgemuth et al, Biophys J, In Press





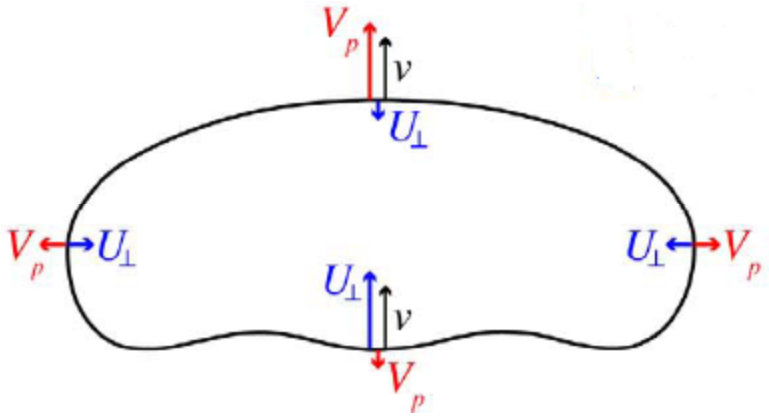
Maybe what could help is if both polymerization and inward flow are graded:

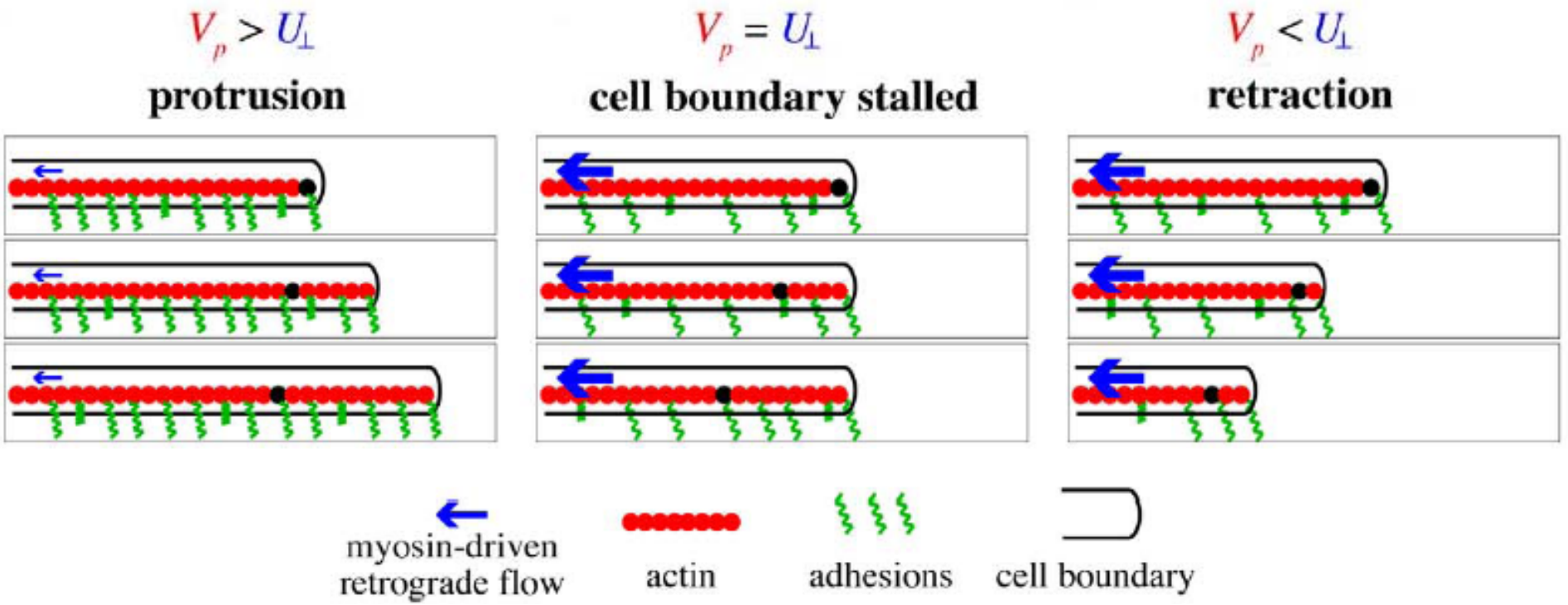
Barnhard et al, PLoS Biology, 2011

v = cell boundary protrusion/retraction rate

V_p = actin polymerization rate

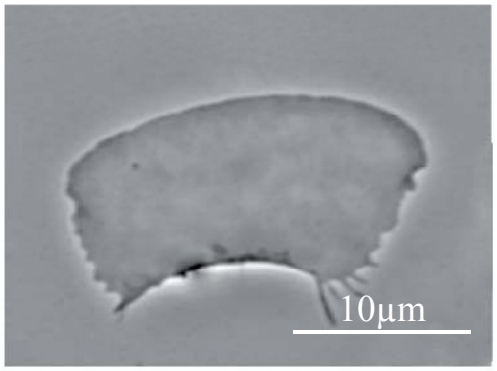
$U_\perp$ = myosin-driven retrograde flow rate

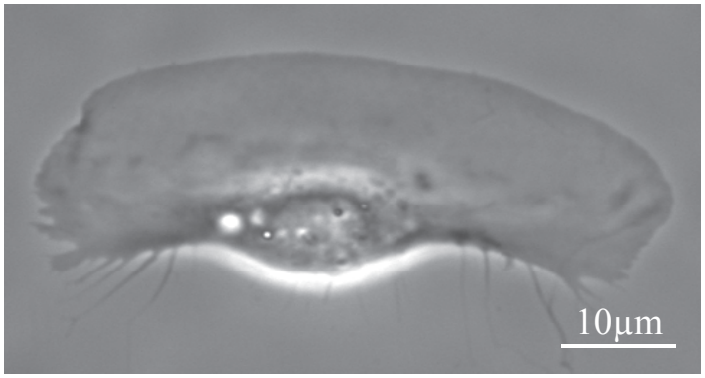




In fact, in lamellipodial fragments…

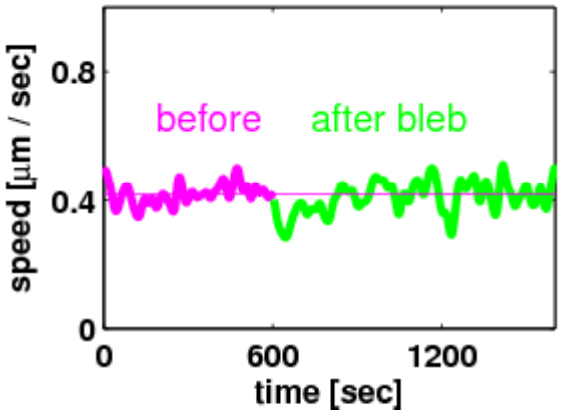
Ofer et al 2011, PNAS, In Revision

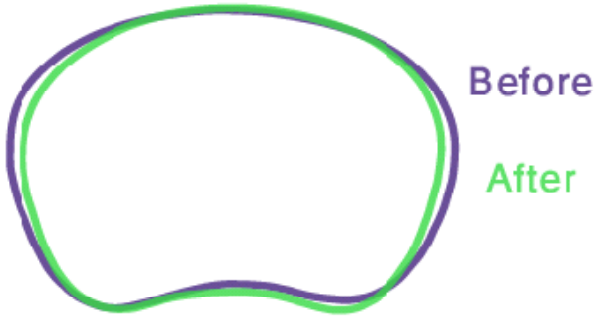




…myosin is too weak and does not play a role:

Inhibiting myosin does not change shape/speed:





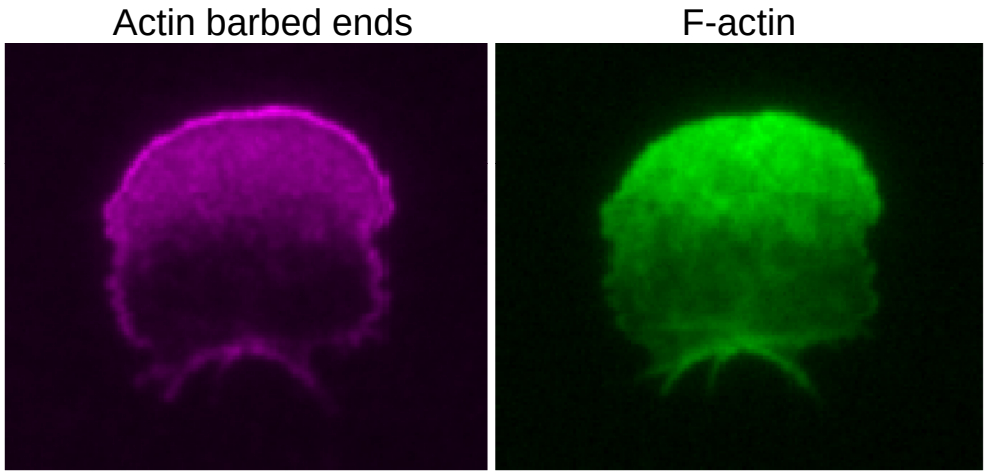
N=20

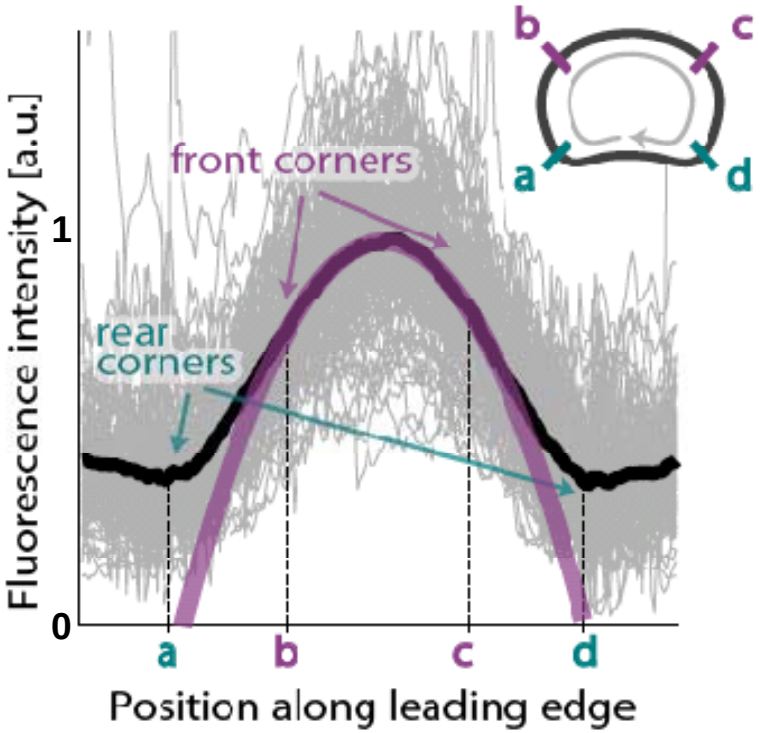
Mean shape before/after treatment

with myo-inhibitor blebistatin

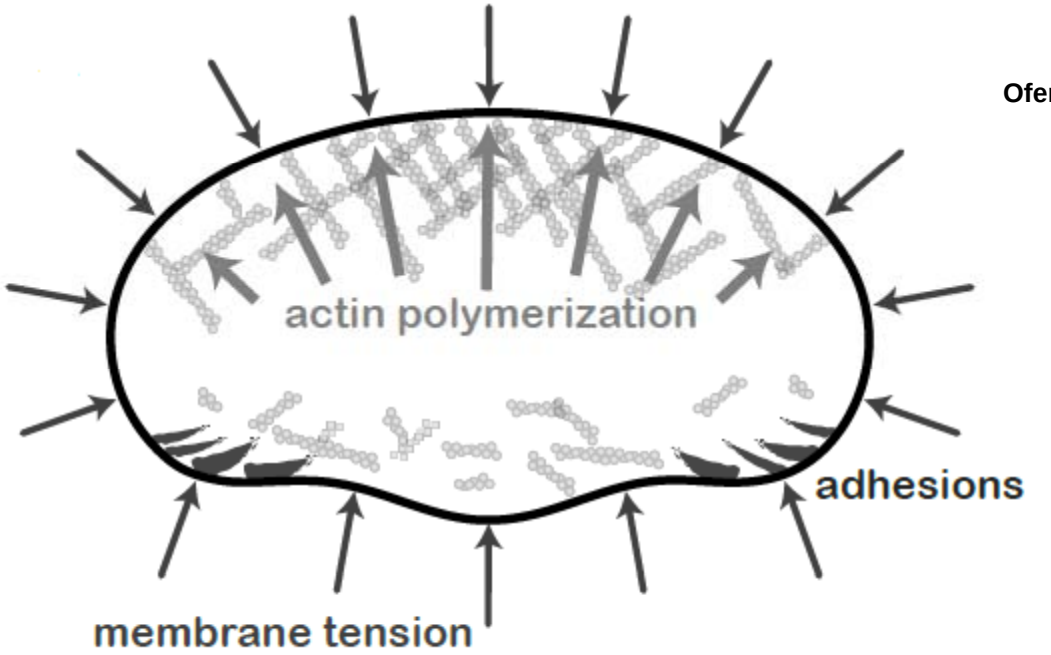
F-actin distribution at the leading edge is graded

Ofer et al 2011, PNAS, In Revision

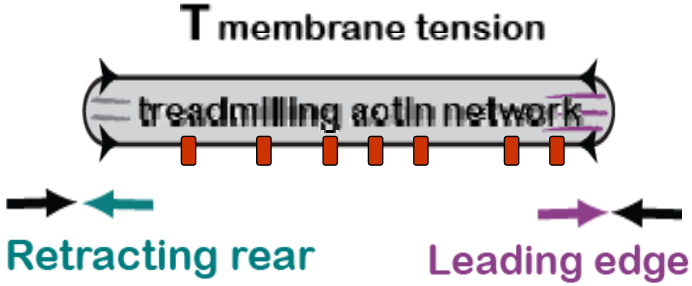




Ofer et al 2011, PNAS, In Revision



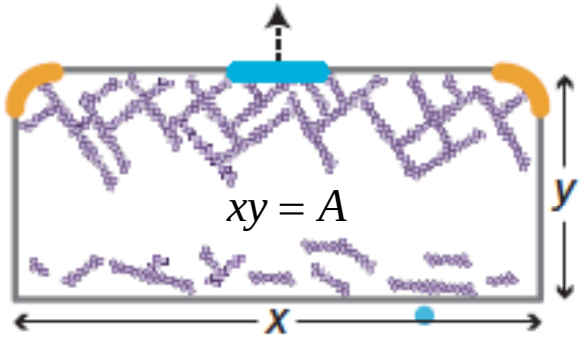
Model: membrane tension stalls actin filaments at the sides.
Higher F-actin density at the center provides protrusion.
At the rear, membrane tension pushes forward disassembling actin network.

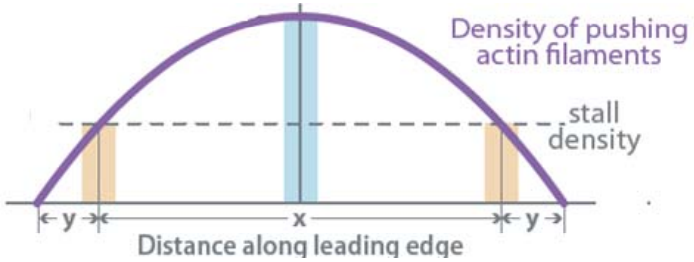


adhesions to the substrate

Quantitatively: membrane tension stalls actin filaments at the sides.

Ofer et al 2011, PNAS, In Revision





$$B(s) = B_0\left(1-\left(\frac{s}{y+x/2}\right)^2\right)$$

$$B_0\left(1-\left(\frac{x/2}{y+x/2}\right)^2\right)$$

Front corners are stalled:

$$f_{stall}B_0\left(1-\left(\frac{(x/2)}{y+(x/2)}\right)^2\right)=T$$

$$1-\left(\frac{1}{1+2y^2/A}\right)^2=\frac{T}{B_0 f_{stall}}$$

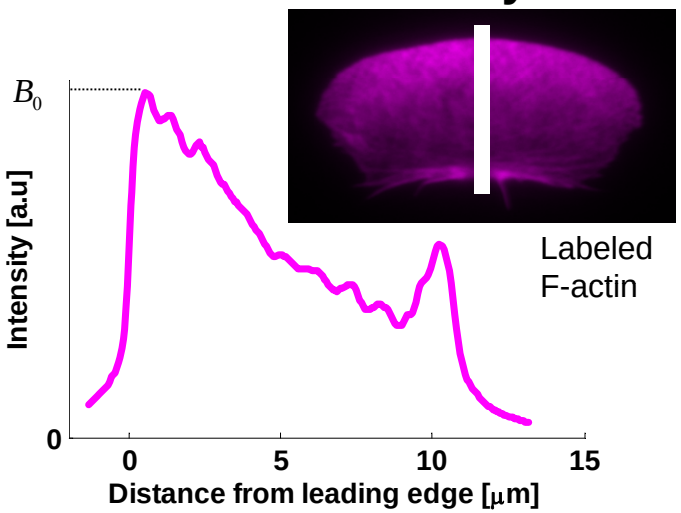
y	front-to-back distance
T	membrane tension
B_0	barbed end density (front center)
f_{stall}	stall force (per filament)
A	area

y - ? T - ?

At the rear, actin network resistance to crushing is balanced by membrane tension.

Ofer et al 2011, PNAS, In Revision

Actin meshwork density



$$B_{rear} = B_0\left(1-\frac{y}{V\tau}\right)$$

Filaments at the rear are broken by the membrane tension; force needed to crush the network is ~ density

$$T = kB_{rear}$$

$$kB_0\left(1-\frac{y}{V\tau}\right) = T$$

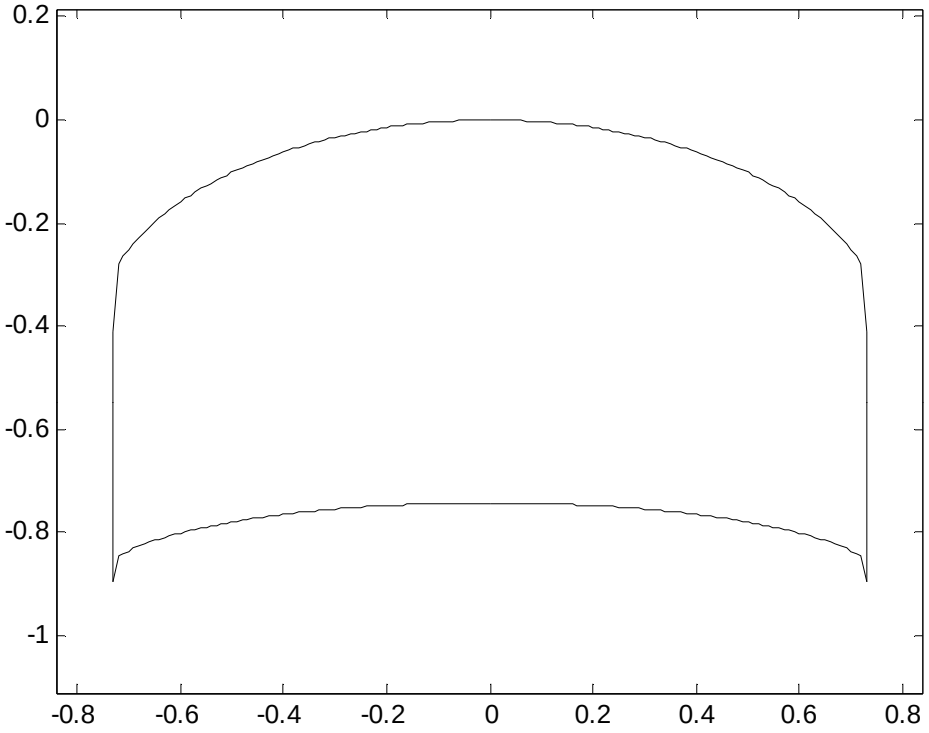
$$1-\left(\frac{1}{1+2y^2/A}\right)^2 = \frac{T}{B_0 f_{stall}}$$

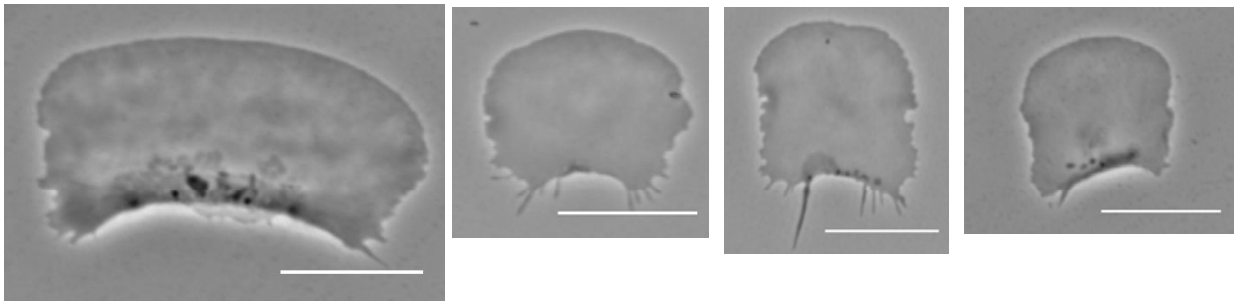
$$1-\frac{y}{V\tau} = \frac{T}{B_0 f_{stall}}\frac{f_{stall}}{k}$$

B_0	barbed end density (front center)
V	cell speed
τ	disassembly time
k	breaking force (per filament)
f_{stall}	stall force (per filament)
y	front-to-back distance
A	area

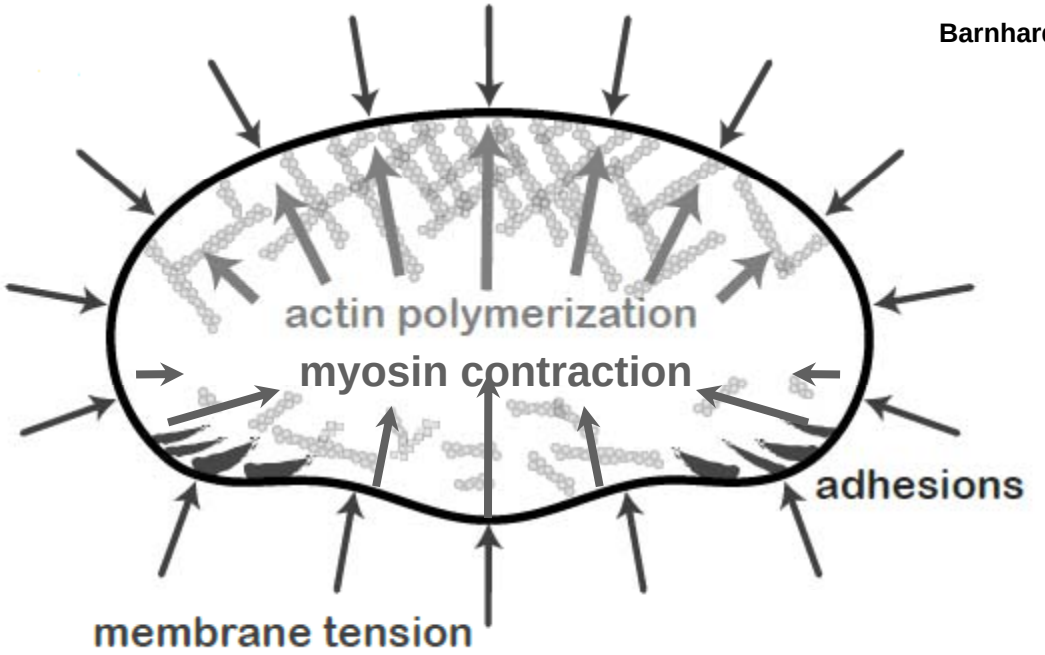
Predicted and observed fragment shapes:

Ofer et al 2011, PNAS, In Revision

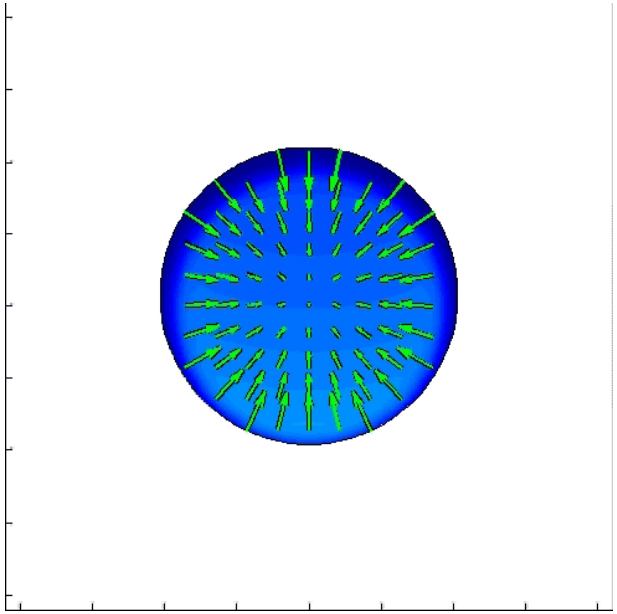




Barnhard et al, PLoS Biology, 2011

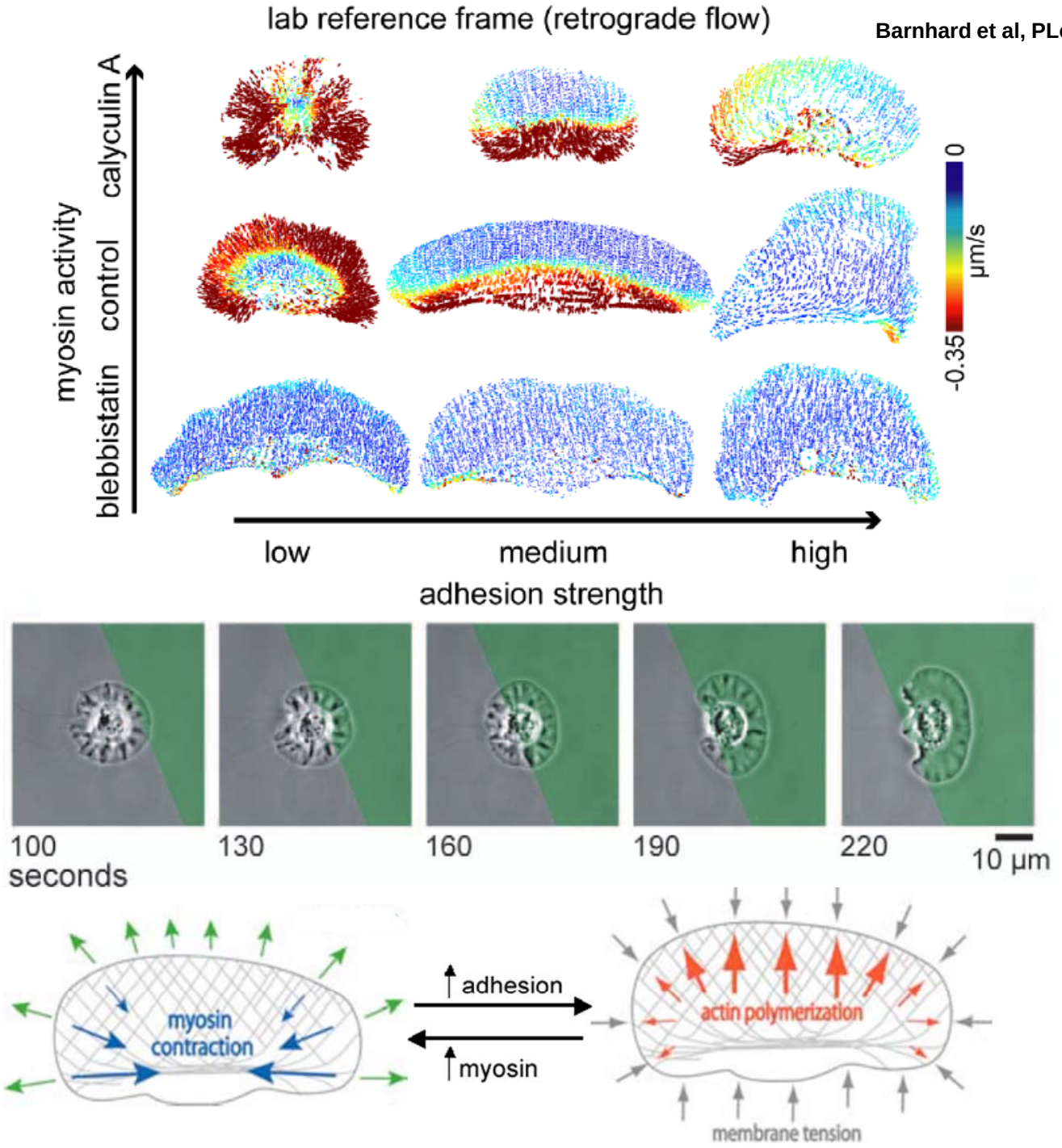


Model: membrane tension stalls actin filaments at the sides + myosin pulls them in.
Higher F-actin density at the center provides protrusion.
At the rear, membrane tension pushes + myosin pulls disassembling actin network.



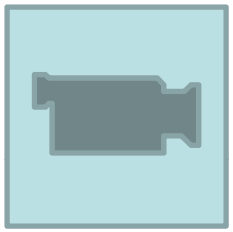
Wolgemuth et al, Biophys J, In Press

Barnhard et al, PLoS Biology, 2011



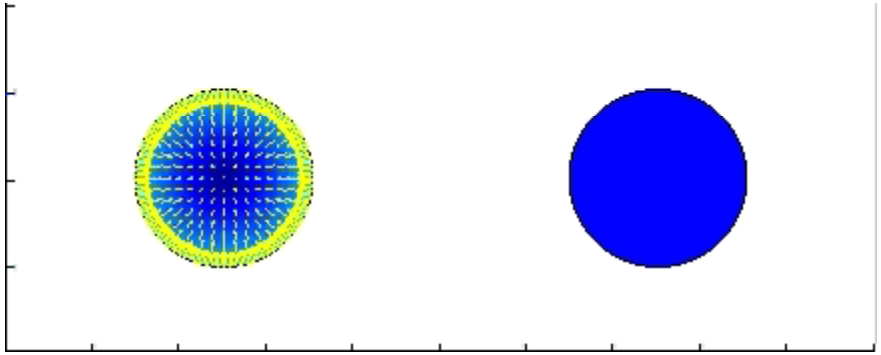
How does the cell change its migration direction?
What asymmetries in internal organization occur?
What are the mechanics and feedbacks underlying these asymmetries?

Allen et al, In Progress



Spontaneous turning:

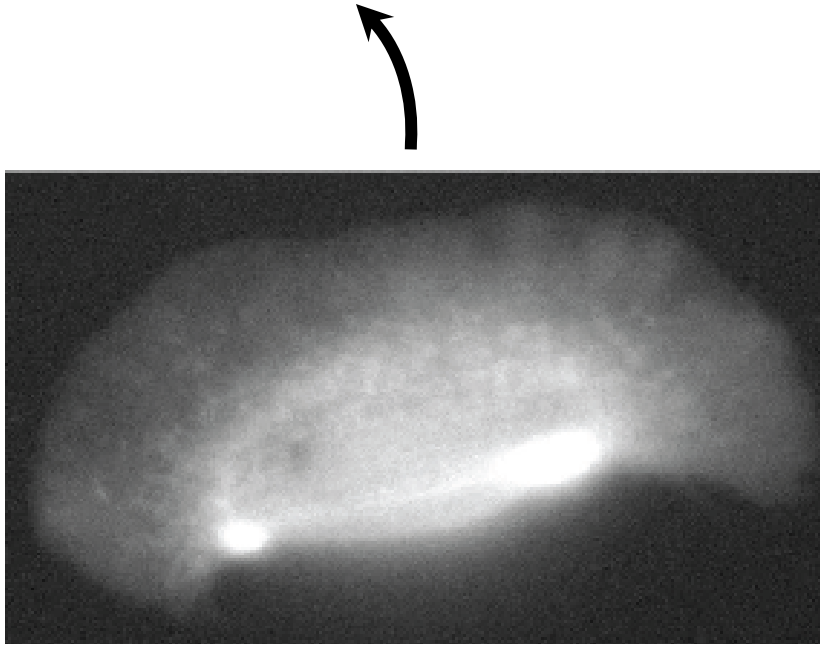
Hypothesis: higher myosin concentration at one side creates inward flow immobilizing that side, so the cell pivots around it.

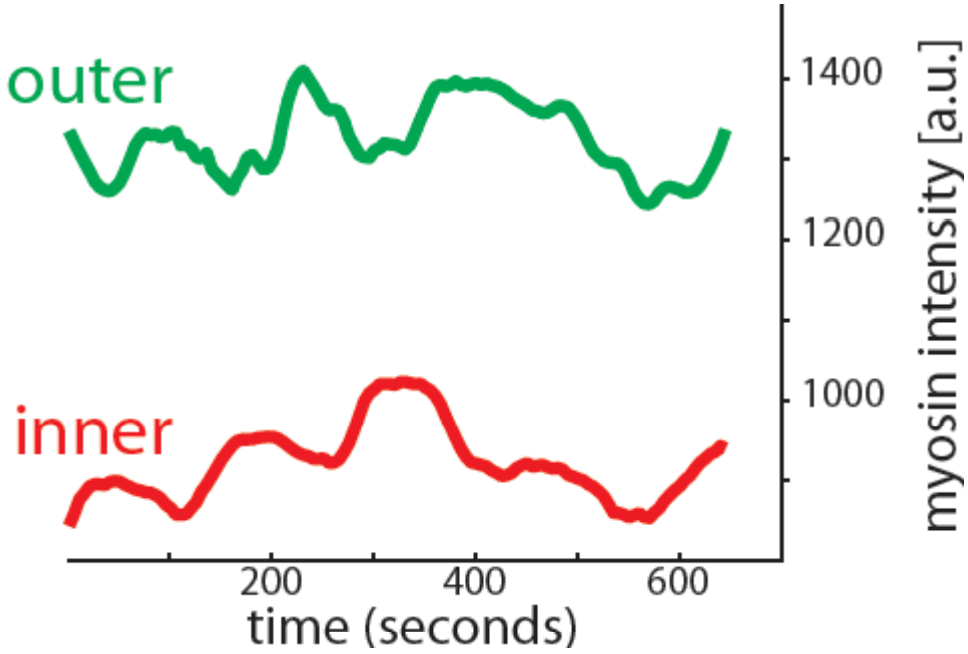


Wolgemuth et al, Unpublished

However, myosin is actually higher at the faster edge:

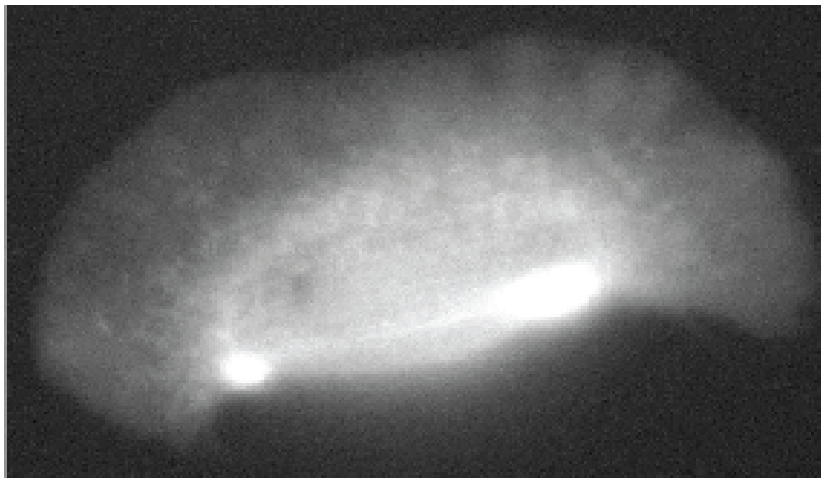
Allen et al, In Progress

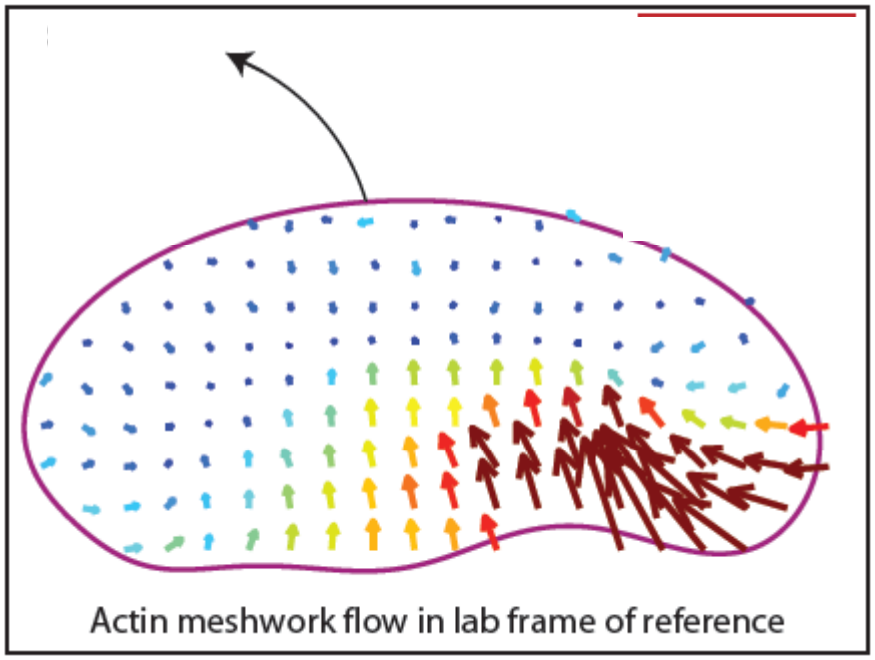


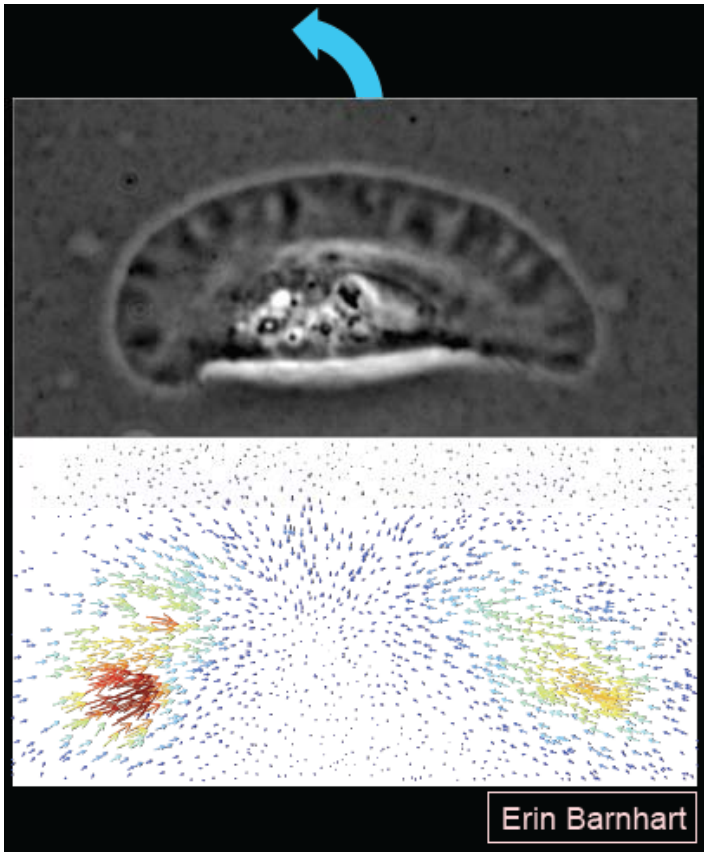


Key asymmetries in internal organization:

Allen et al, In Progress



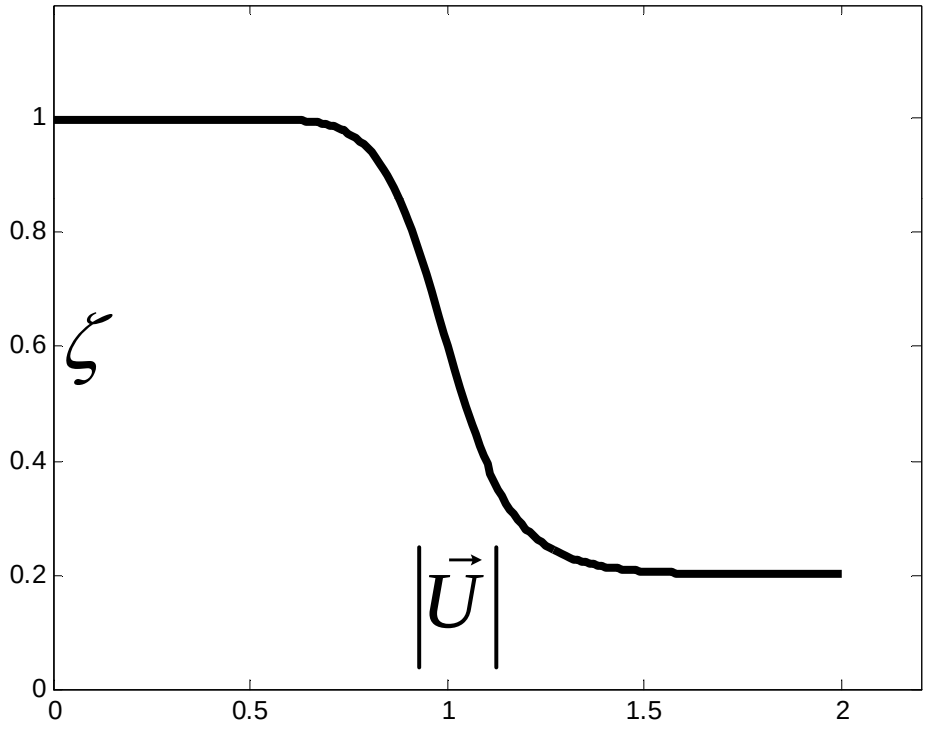




Myosin density and actin flow are higher at the fast side, but traction forces are higher at the slower side

Can the model explain these asymmetries? Turns out, all we need is stick-slip adhesions and an initial fluctuation:

Allen et al, In Progress



$\vec{U}$ **Actin flow velocity**

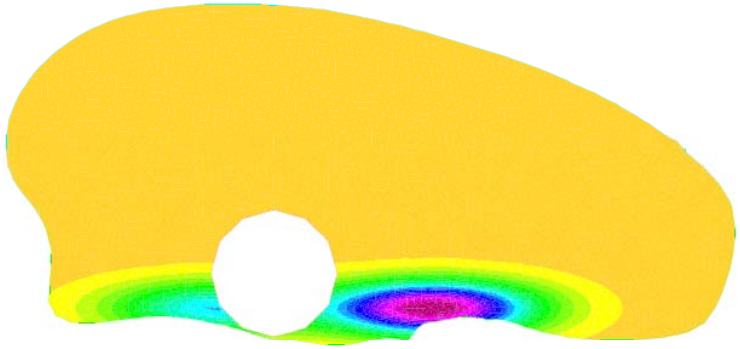
ζ **Adhesion strength**

results of M. Gardel and C. Waterman-Storer, 2008-11

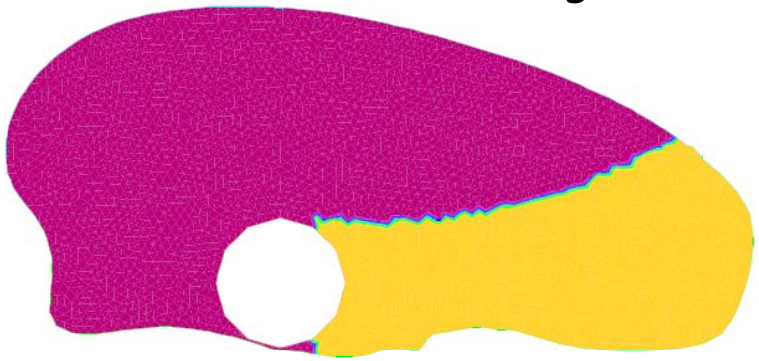
The model predicts that given asymmetric myosin distribution, the actin flow and traction forces are as observed:

Allen et al, In Progress

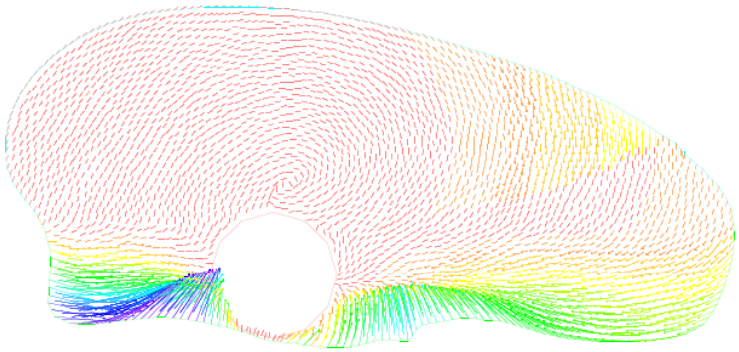
Given myosin distribution:



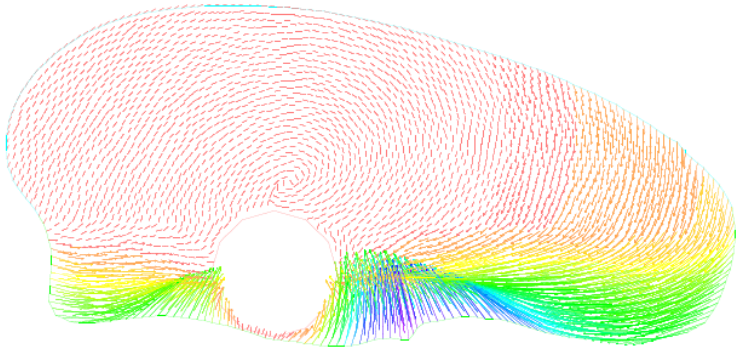
Predicted adhesion strength:



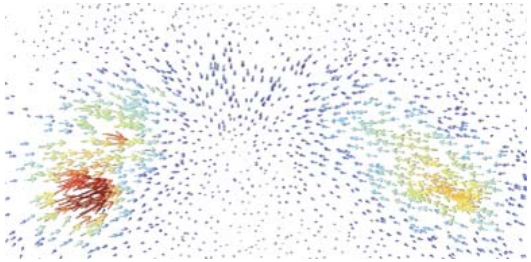
Predicted traction forces:



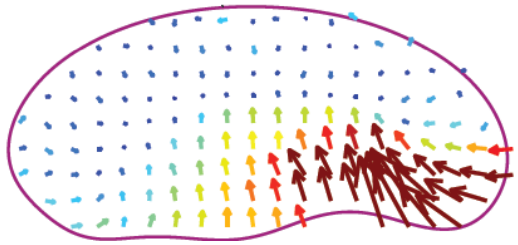
Predicted actin flow:



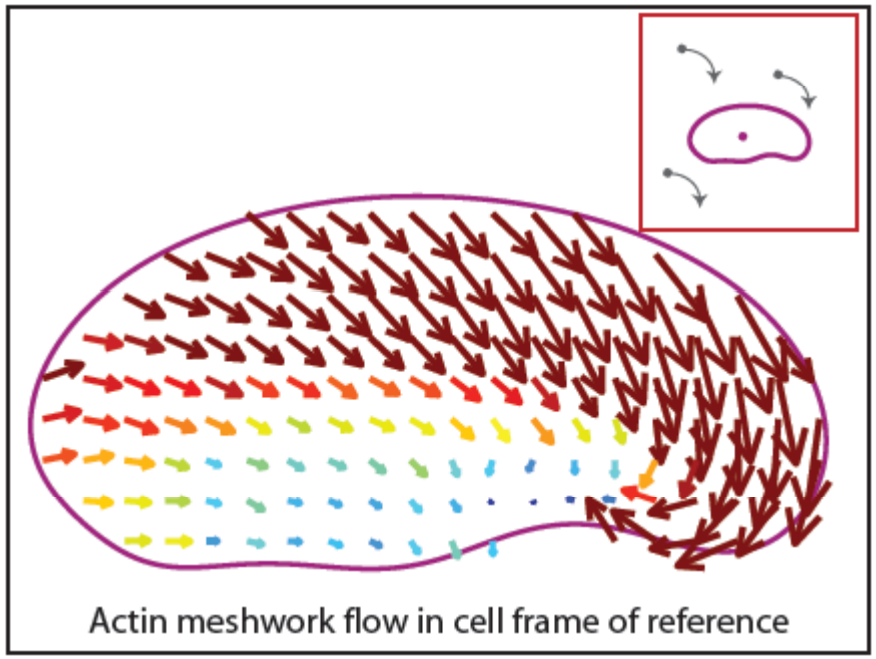
Observed traction forces:

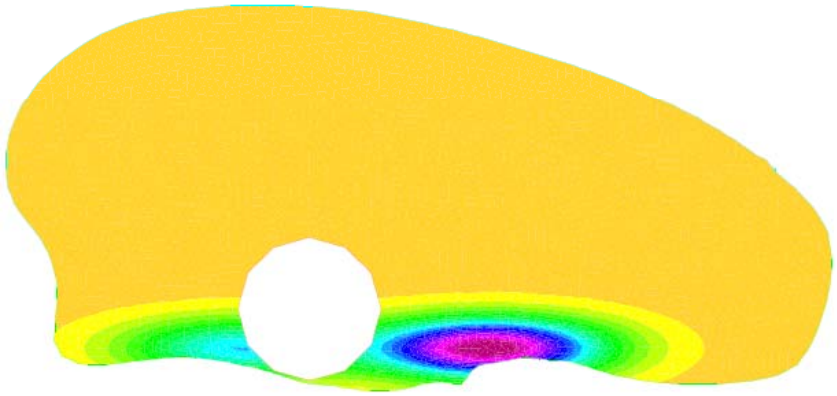


Observed actin flow:



Why is myosin distributed as observed?
Because it is swept to the faster side by the actin flow:



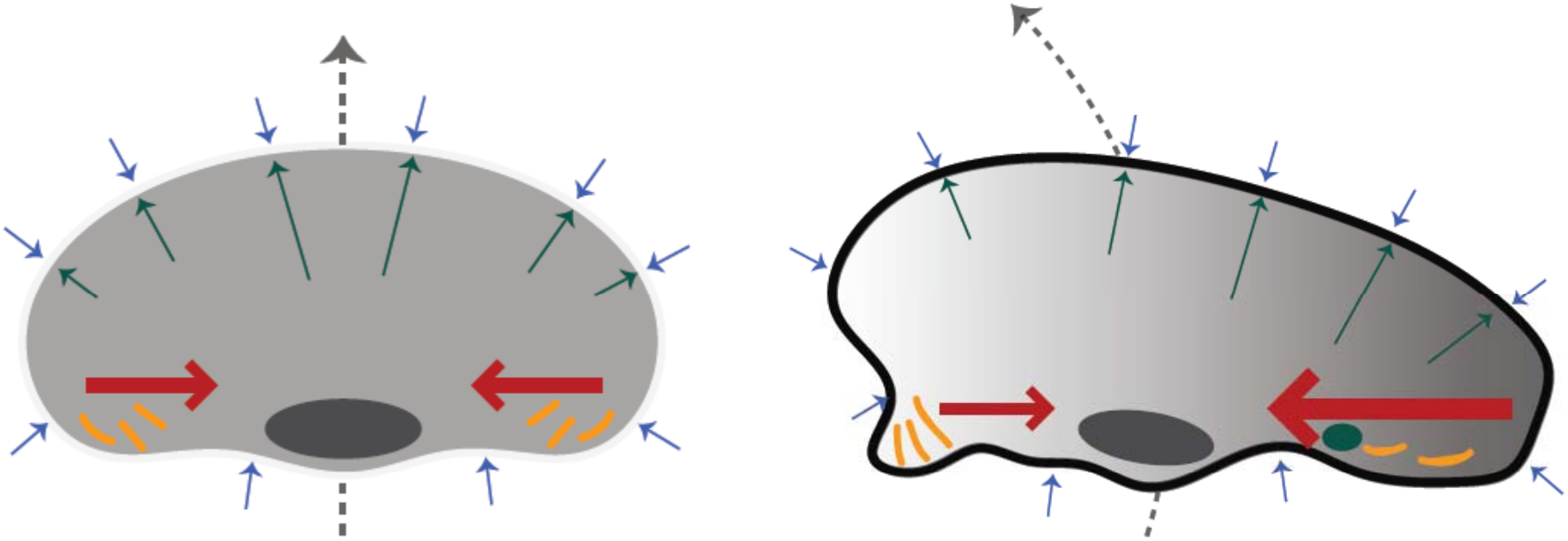


Predicted myosin distribution

$$\frac{\partial M}{\partial t} = D_M \nabla^2 M - \nabla \cdot ((\vec{U} - \vec{V_{cell}}) M)$$

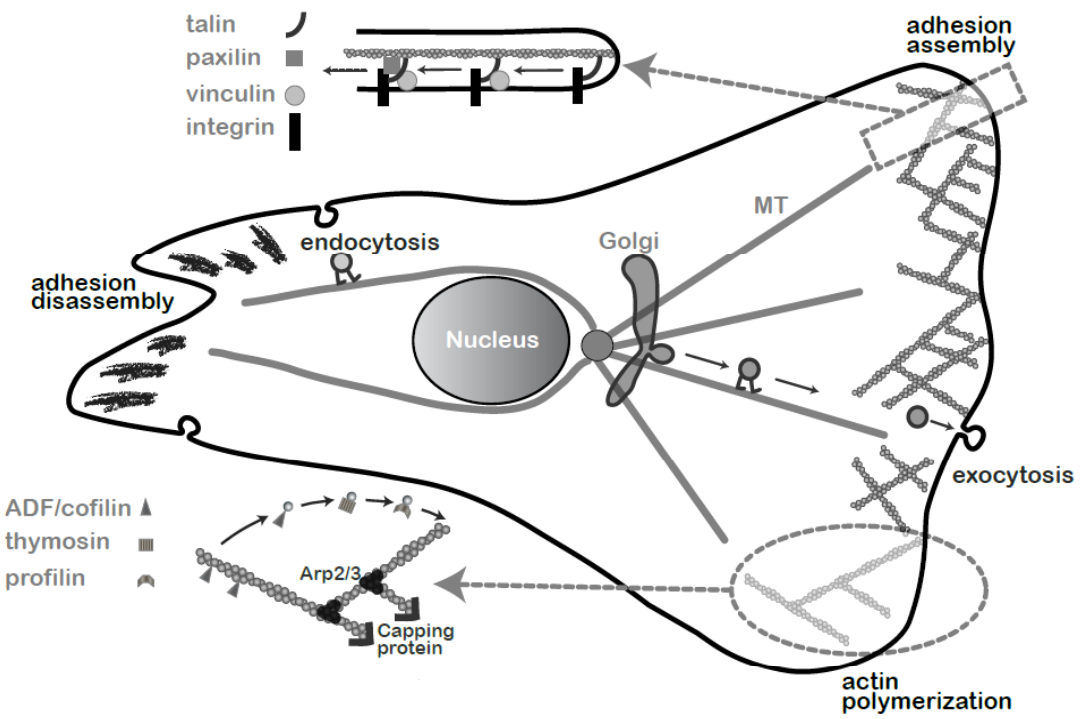
Allen et al, In Progress

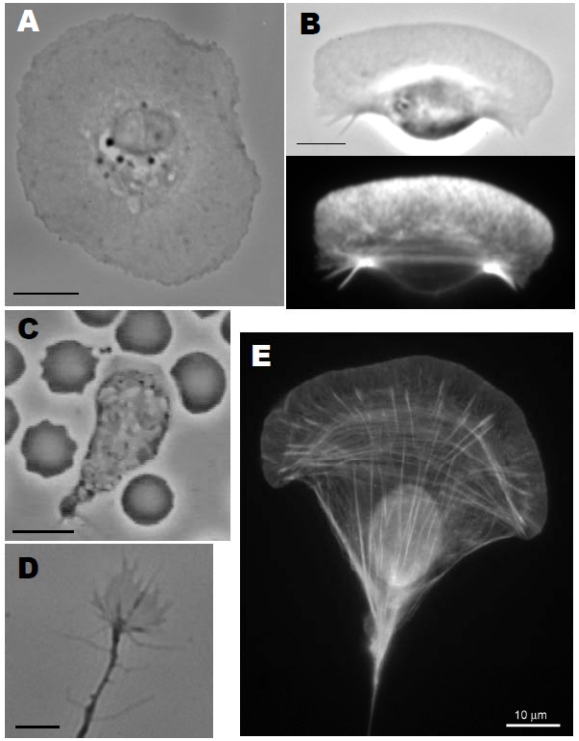
Mechanical feedback of turning:
more myosin at one side accelerates the flow and decreases adhesions.
Respective rear side advances faster re-orienting leading edge machinery, so respective front side advances faster.
Resulting flow in the cell framework sweeps myosin to the faster side.



Allen et al, In Progress

Future: other redundant motility modules, complex cells,…





Mogilner and Keren, Curr Biol 2009

U California at Davis:

Jie Zhu 

Kun-Chun Lee 

E. Barnhart 

Stanford:

J. Theriot 

G. Allen 

Technion:

Kinneret Keren 

Noa Ofer 

U Connecticut:

Charles Wolgemuth 

+ earlier work (BJ 2009) with: ***Boris Rubinstein (UC Davis), Sasha Verkhovsky, Maxime Foruneir (EPFL)***

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