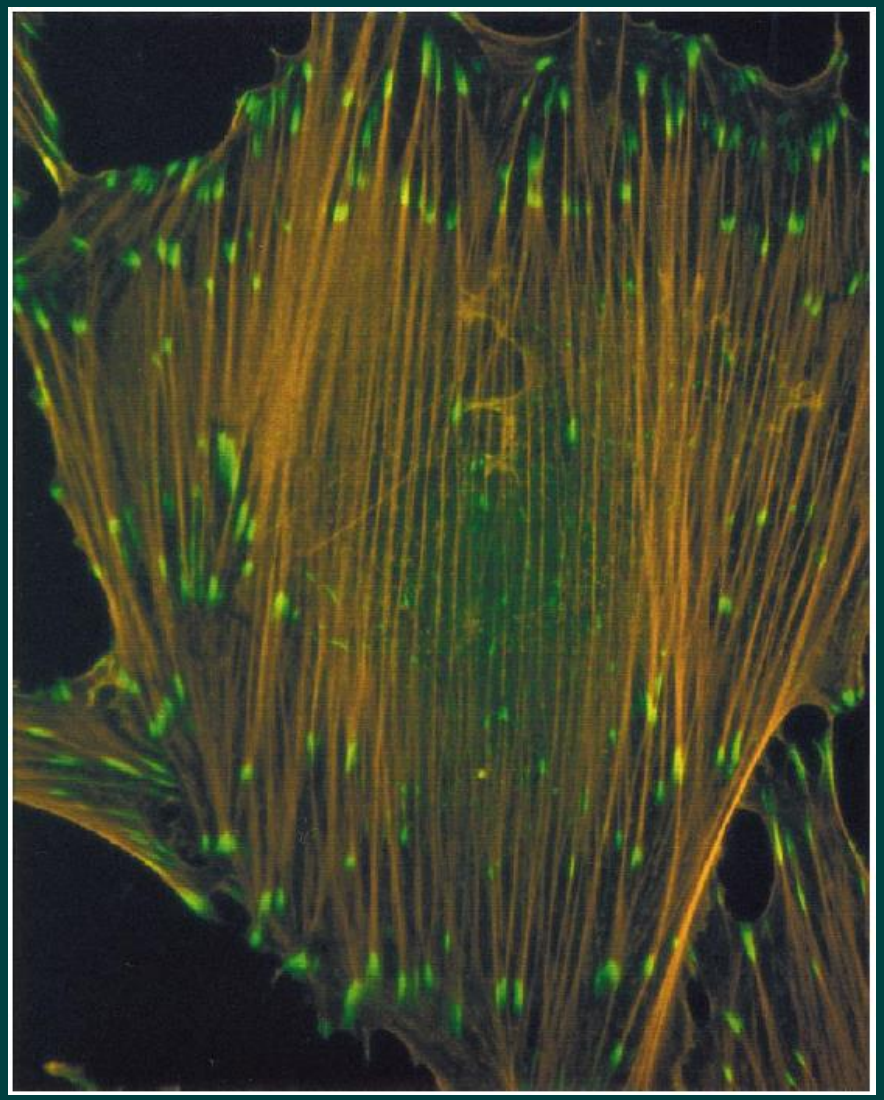
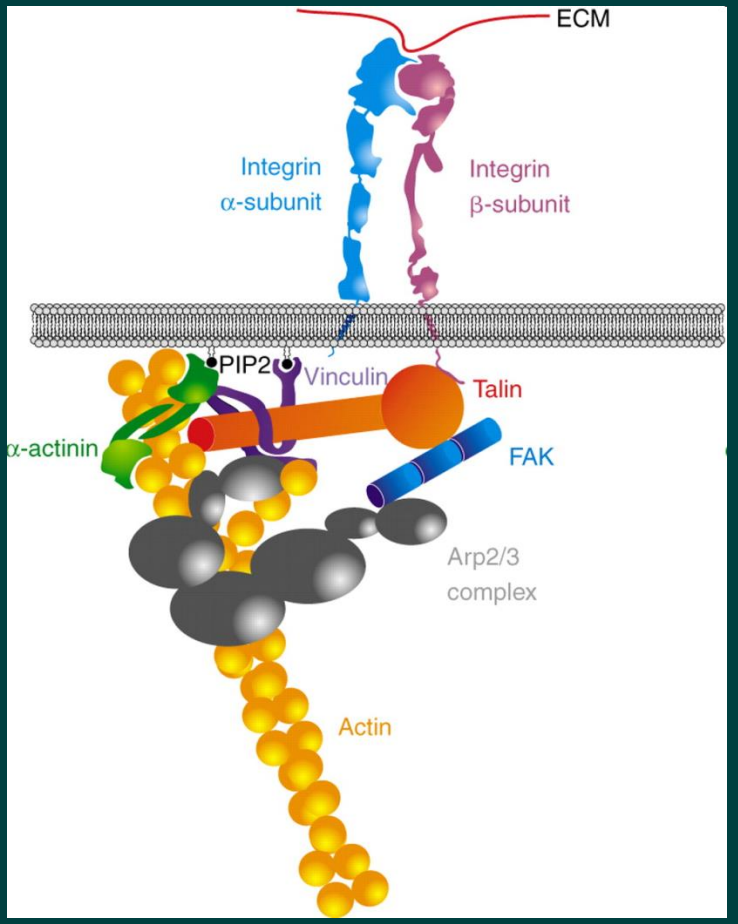
last time: Focal adhesions connect actin filaments to the extracellular matrix

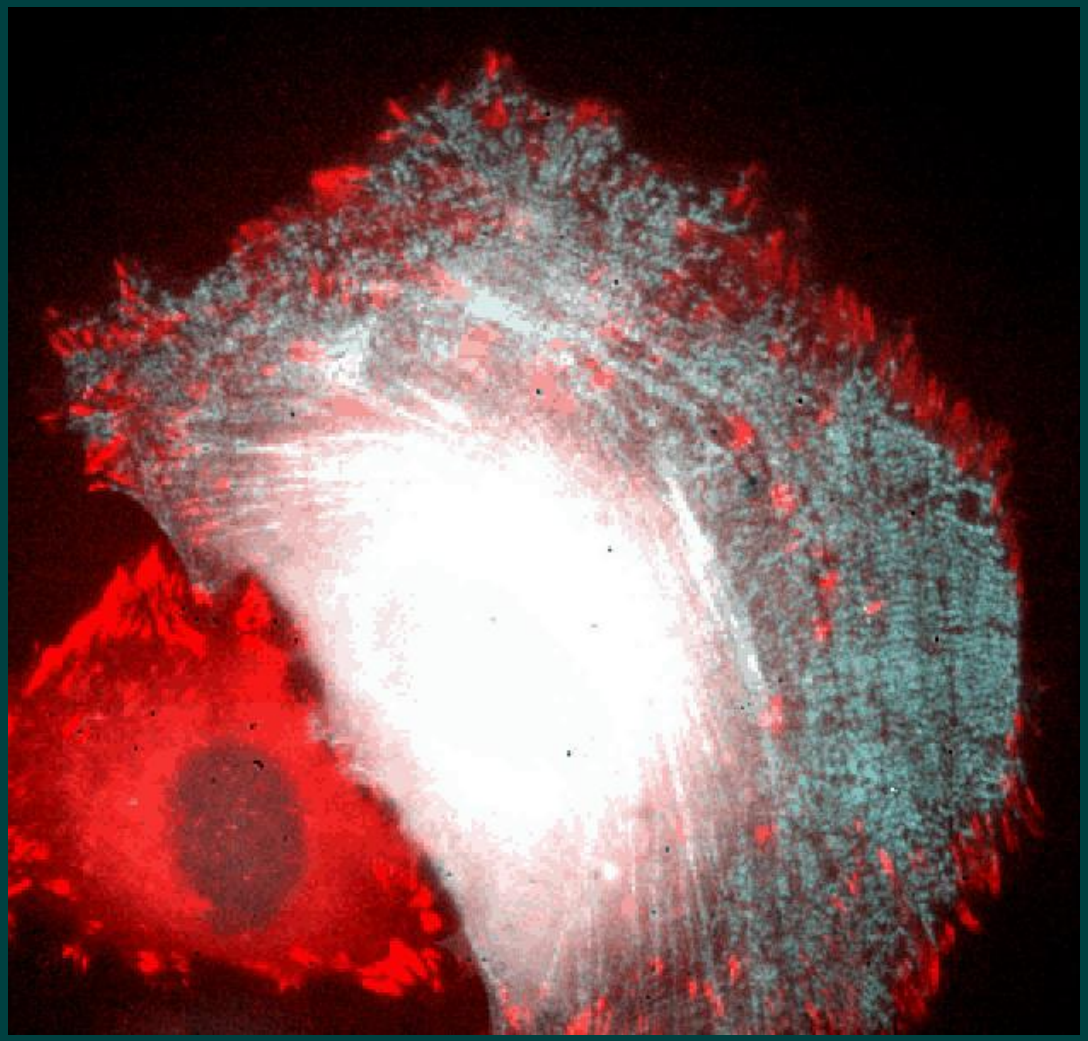


Sastry and Burridge, Exp. Cell Res., 2000



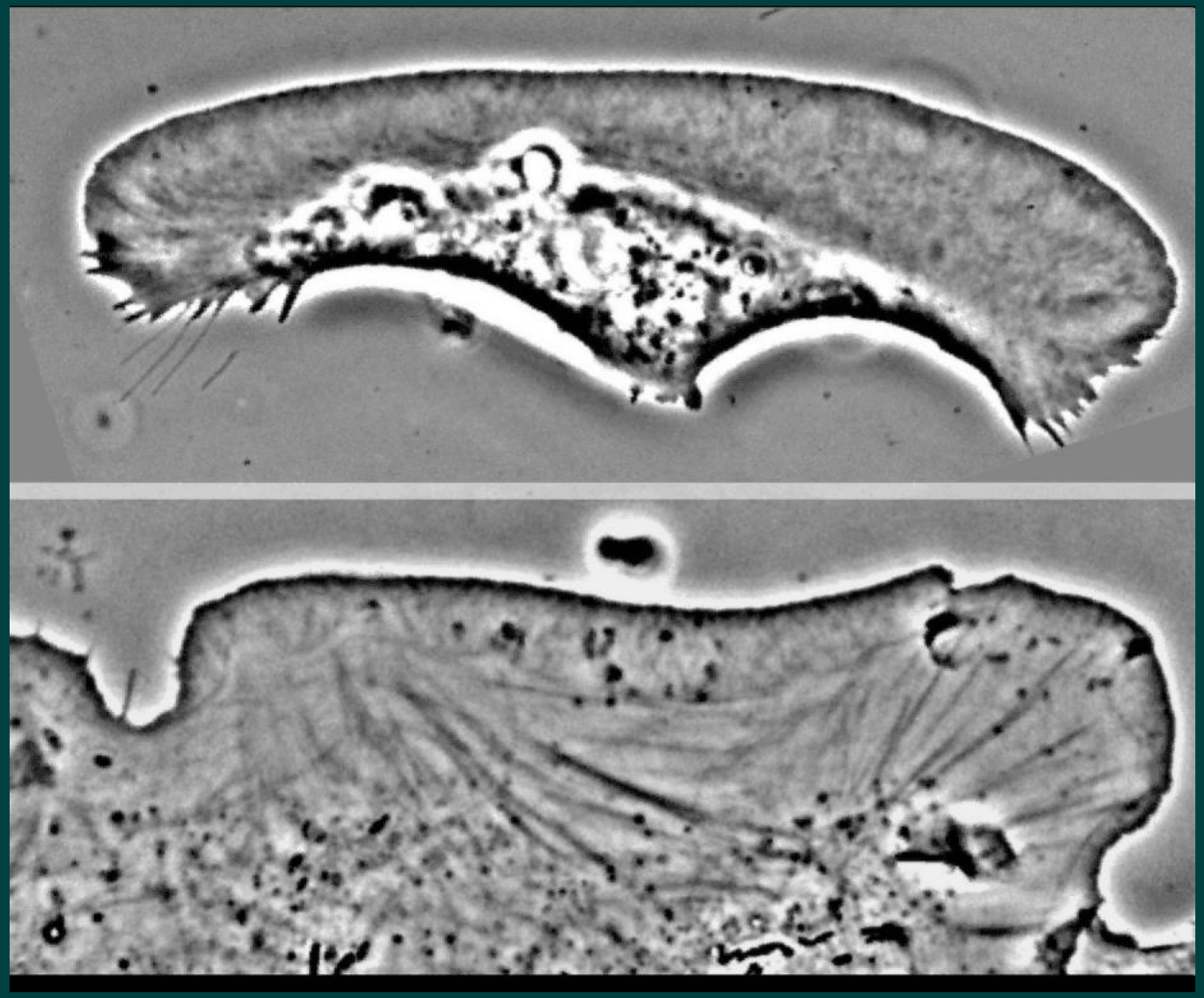
Vicente-Manzanares et al., J.Cell Sci., 2009

Stress fibers contract and slide with respect to stationary adhesions



now: mechanics of cytoskeleton-adhesion connection
motion without specific adhesion
more about polarization mechanisms

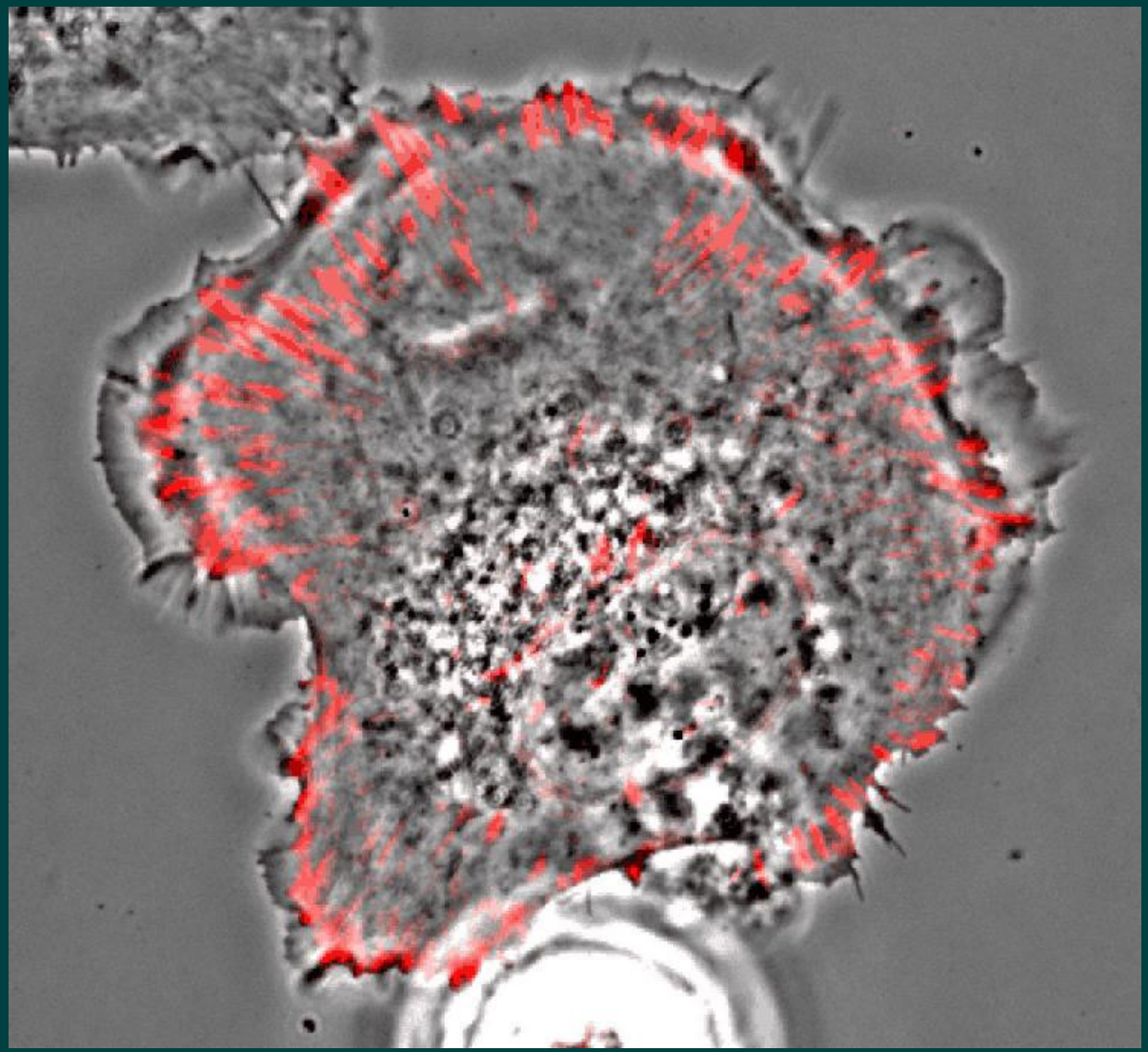
actin moves (retrograde/anterograde flow)
substrate is stationary
adhesions - ?



keratocyte

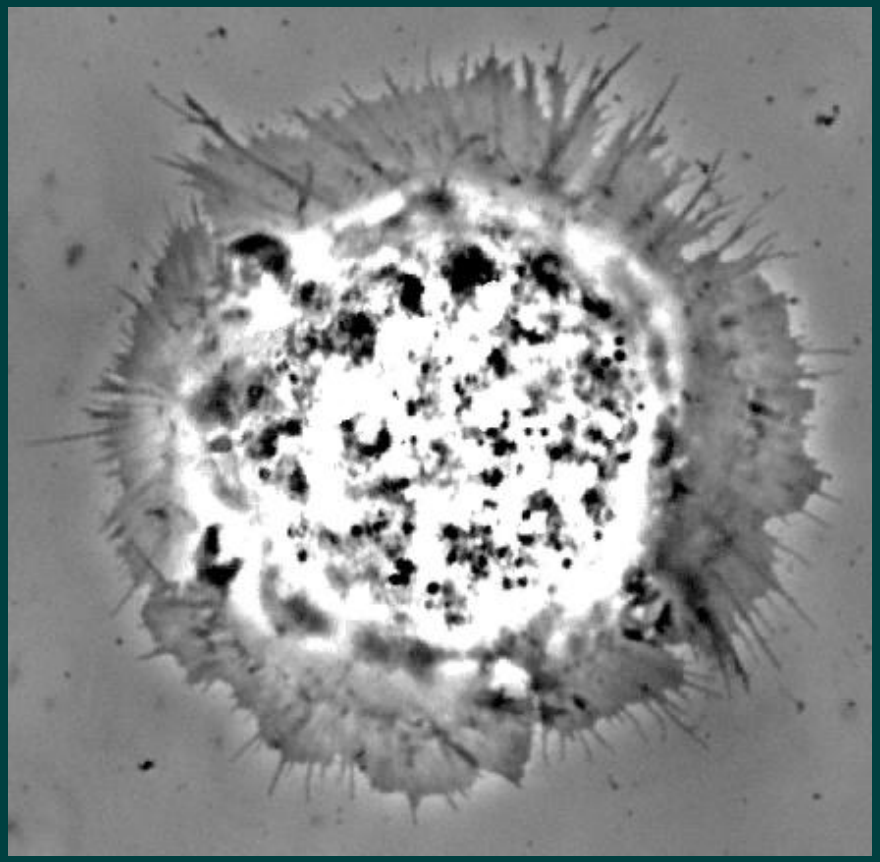
fibroblast

Lamellipodium/lamellum transition is defined by focal adhesions (FA)



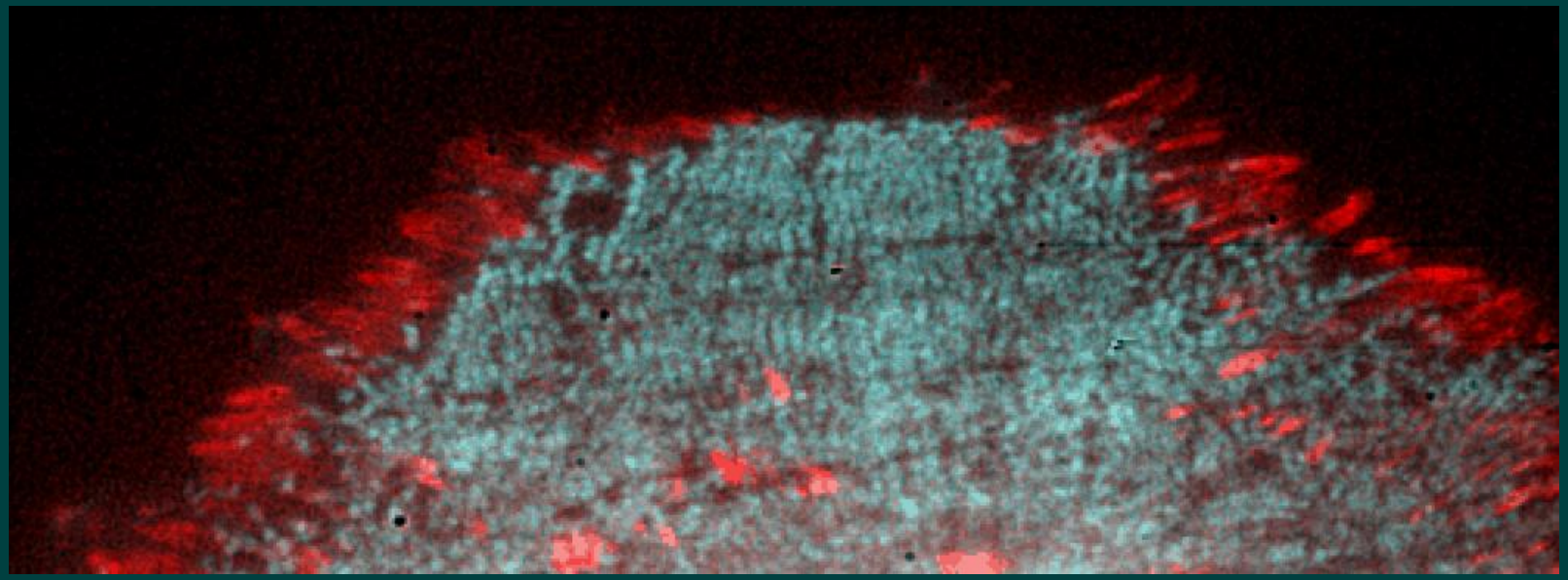
transition moves
with nascent FA

On poly-L-lysin:
no FA and no transition

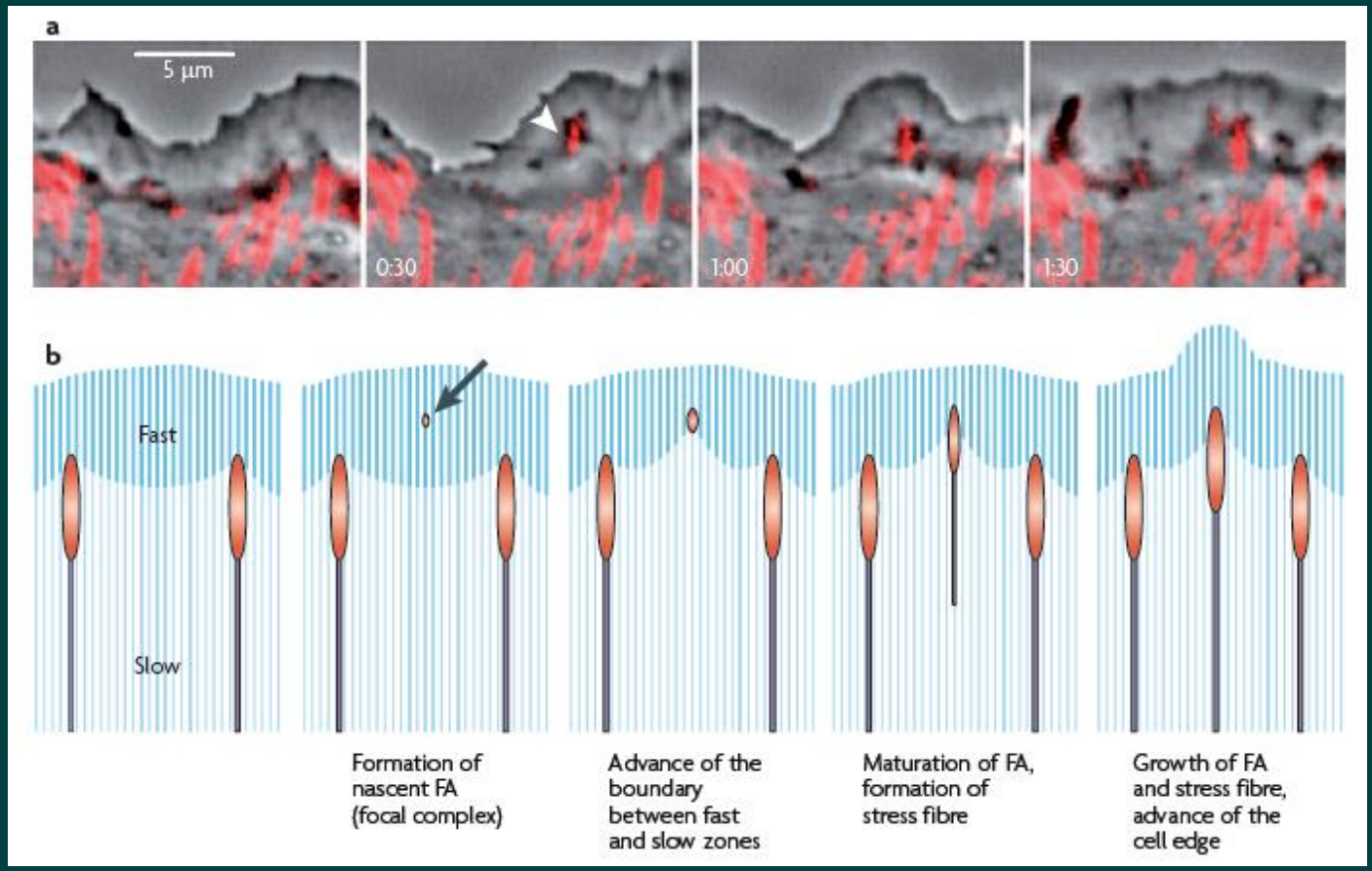


(fast stream of lamellipodial flow breaks at FA)

Stress-fibers contract while focal adhesions are stationary: slow flow continues centripetally to adhesions

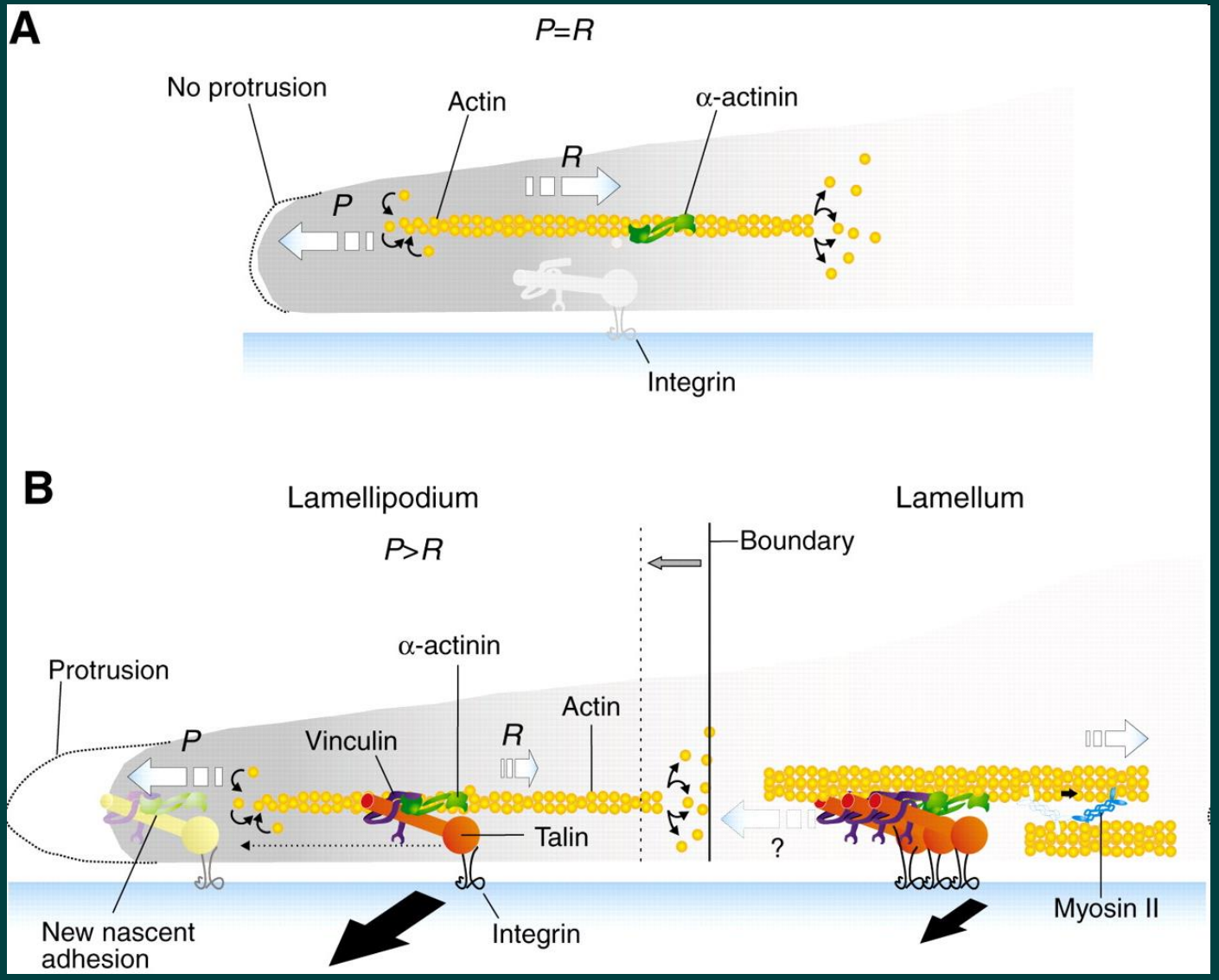


cyclic formation and advance of lamellipodia and adhesions



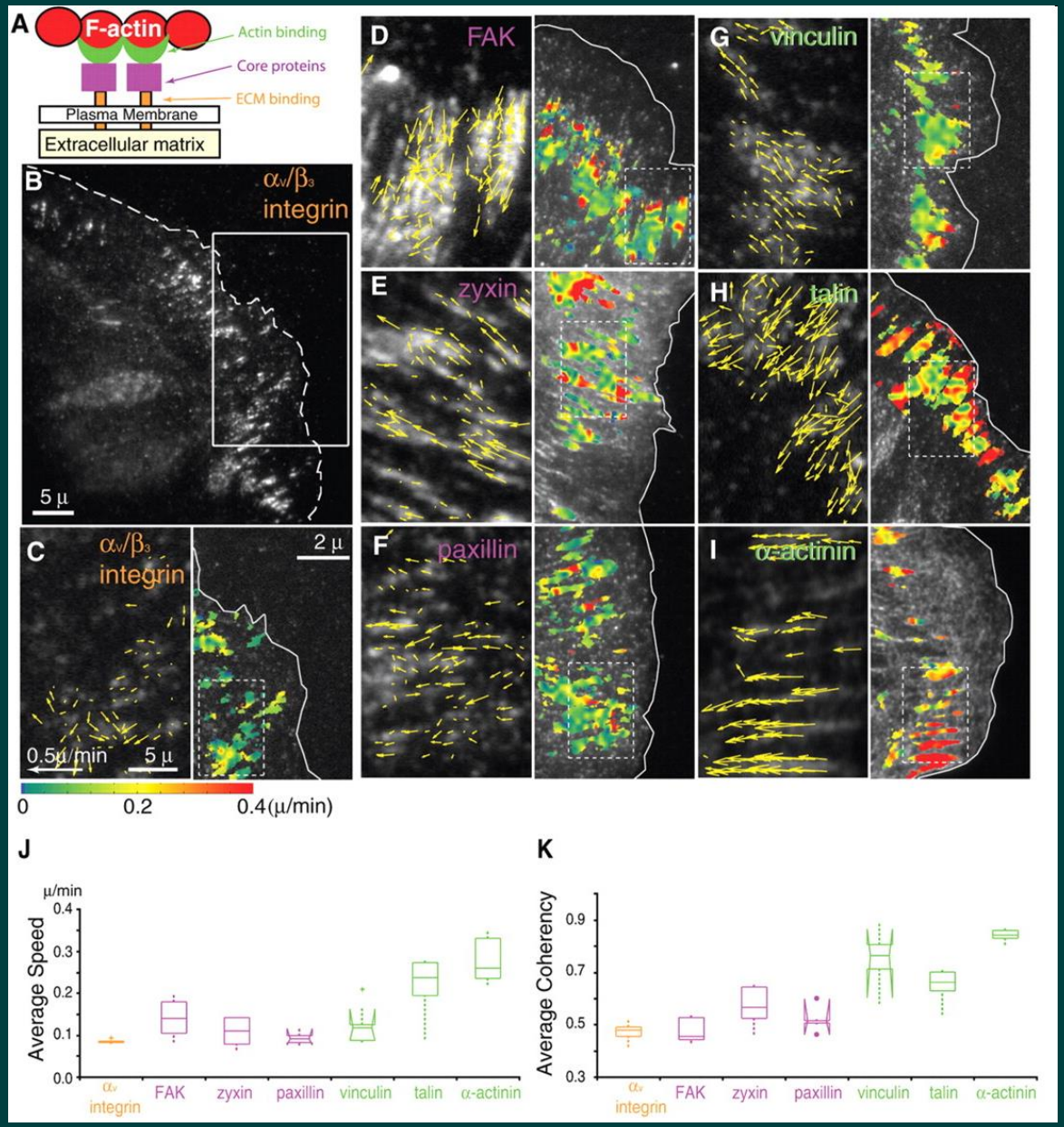
Alexandrova et al., 2008

Adhesions as molecular clutch



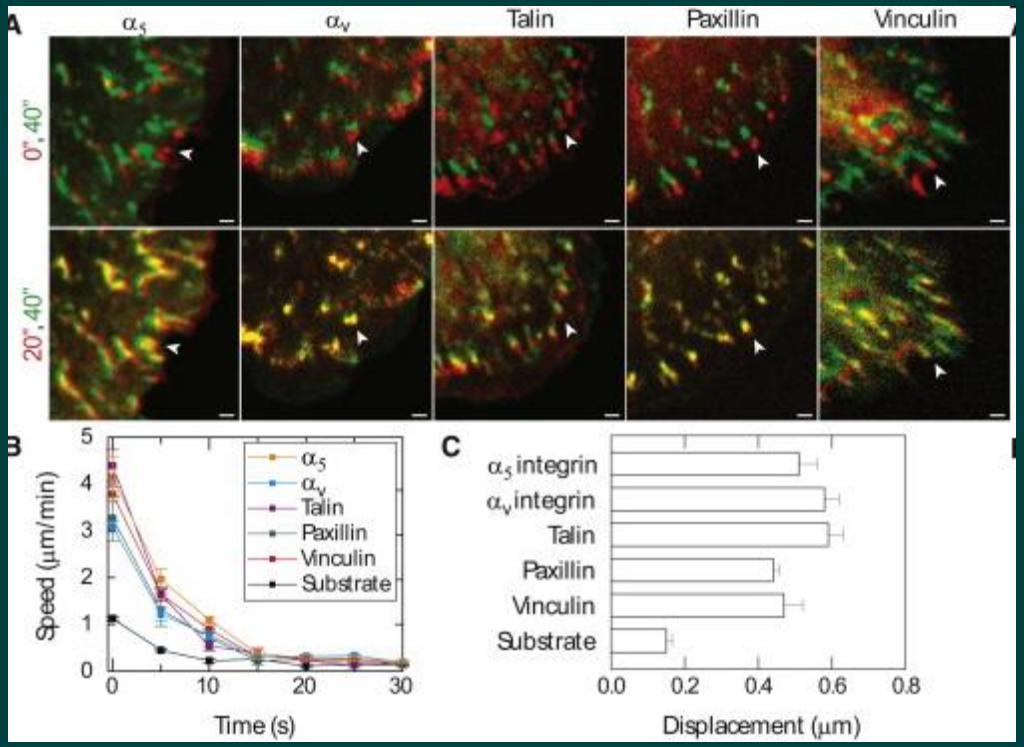
Vicente-Manzanares et al., J.Cell Sci., 2009

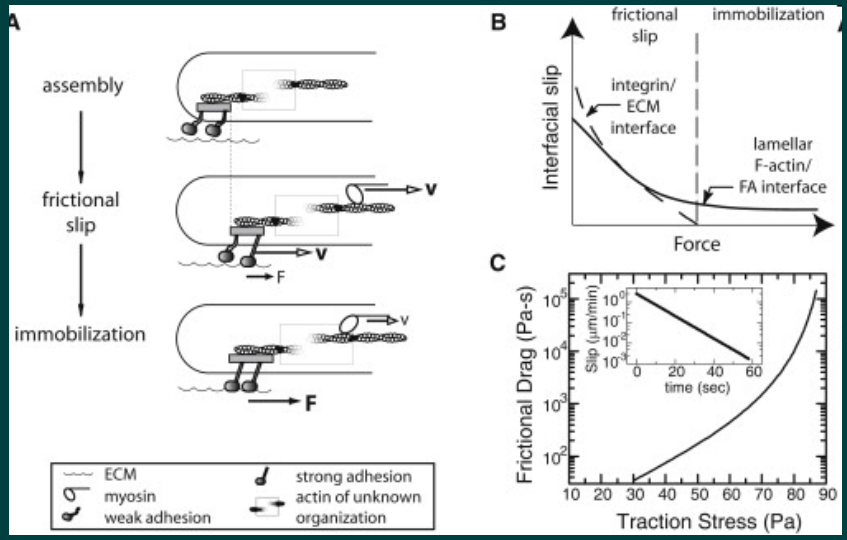
FA proteins move with different velocities (slippage between actin and FA)



Hu et al., Science, 2007

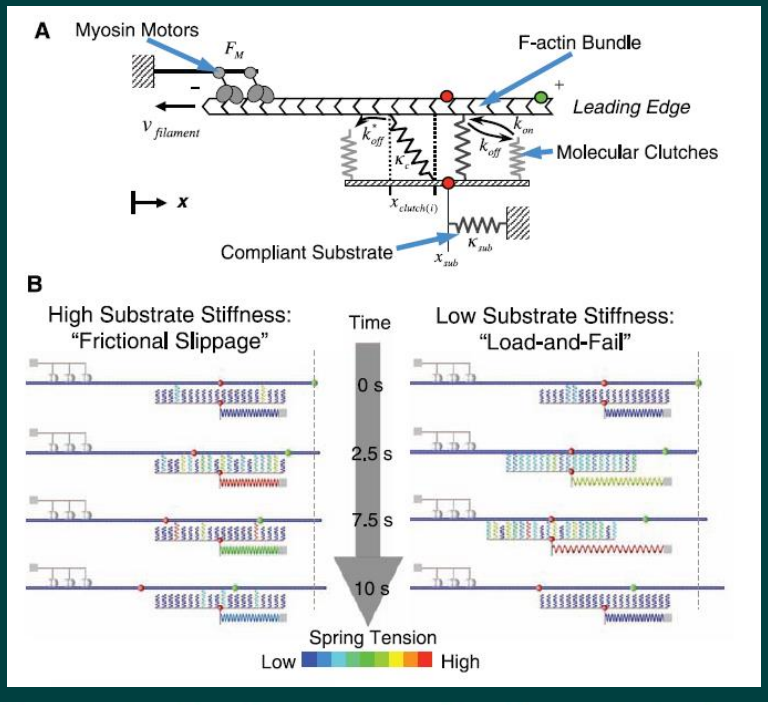
In nascent adhesions, integrins move too,
then become immobilized with the matrix



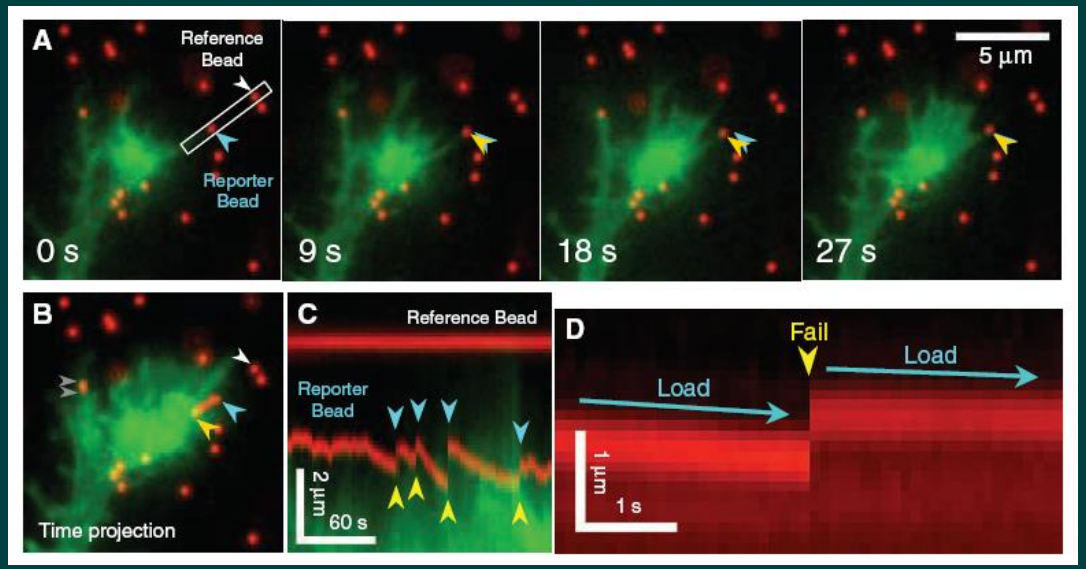


Aratyn-Schaus and Gardel, 2010

Traction forces on the substrate slipping or gripping?

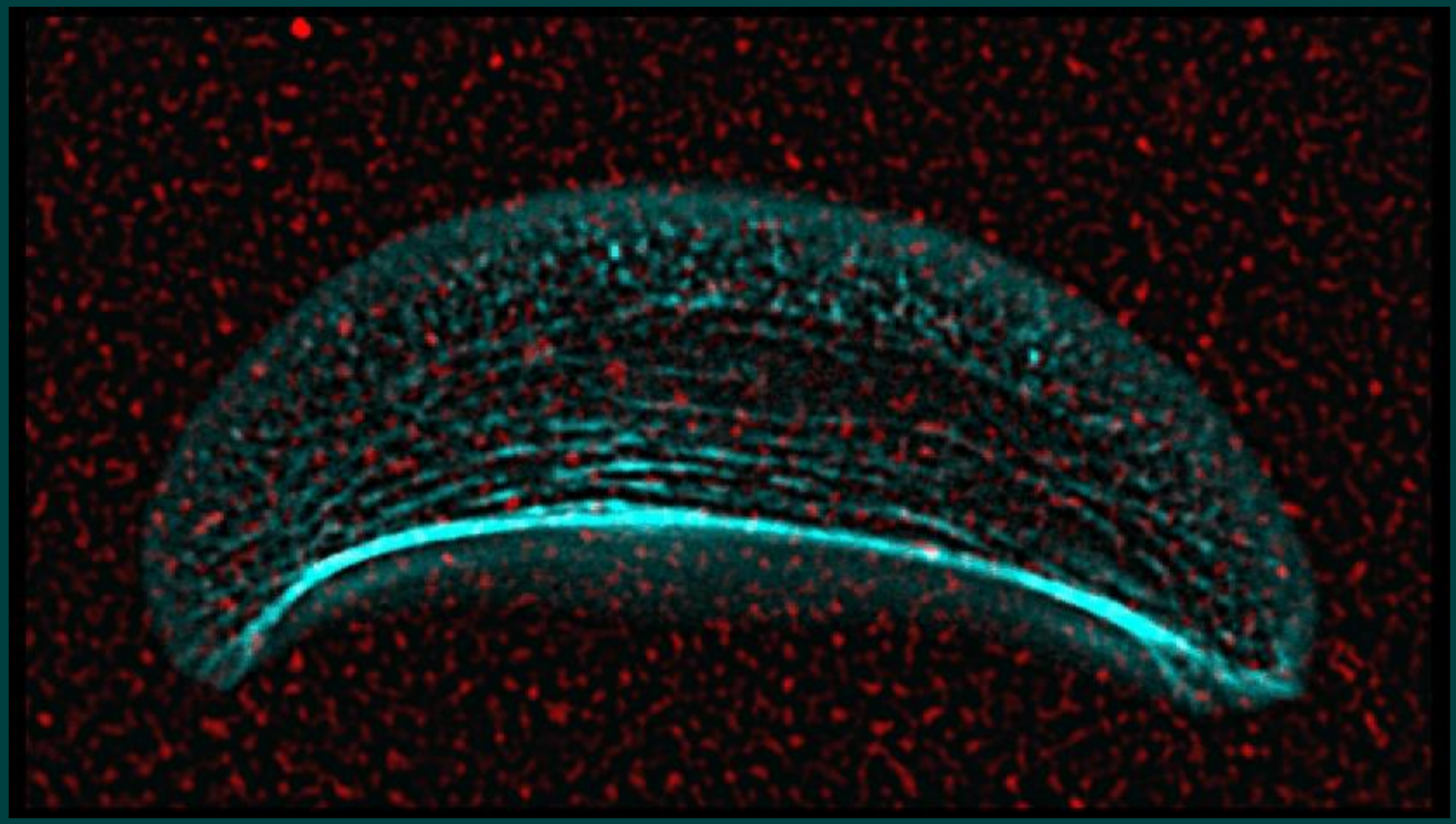


Chan and Odde, 2008



simultaneous mapping of actin motion and traction stress on the substrate

Gelatin substrate (Doyle and Lee)

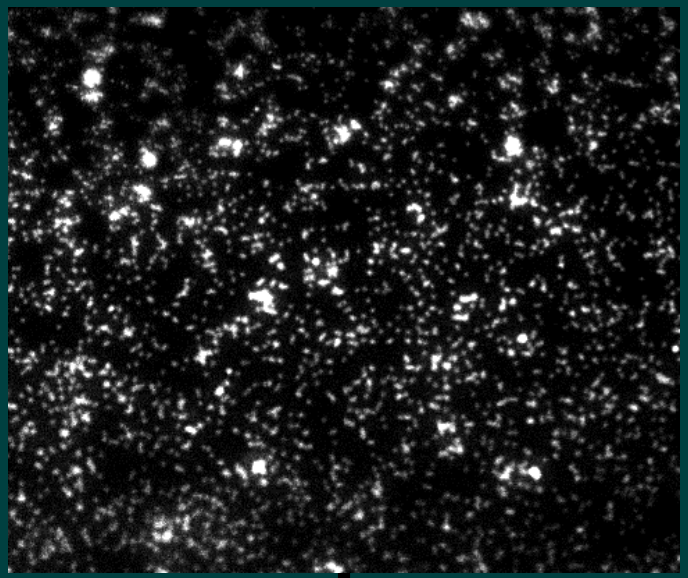


substrate force = (actin velocity relative to the substrate) x
x (viscosity of actin/substrate connection)

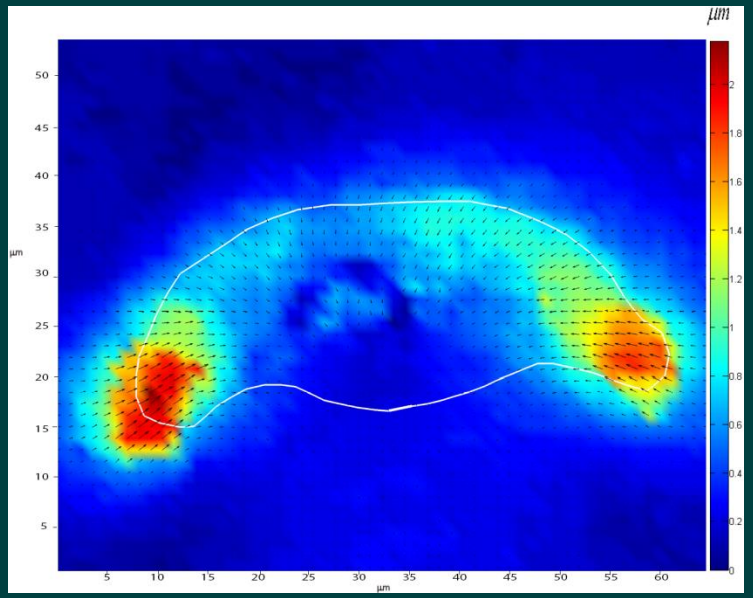
Fournier et al., J Cell Biol, 2010

stress computation

deformed/undeformed

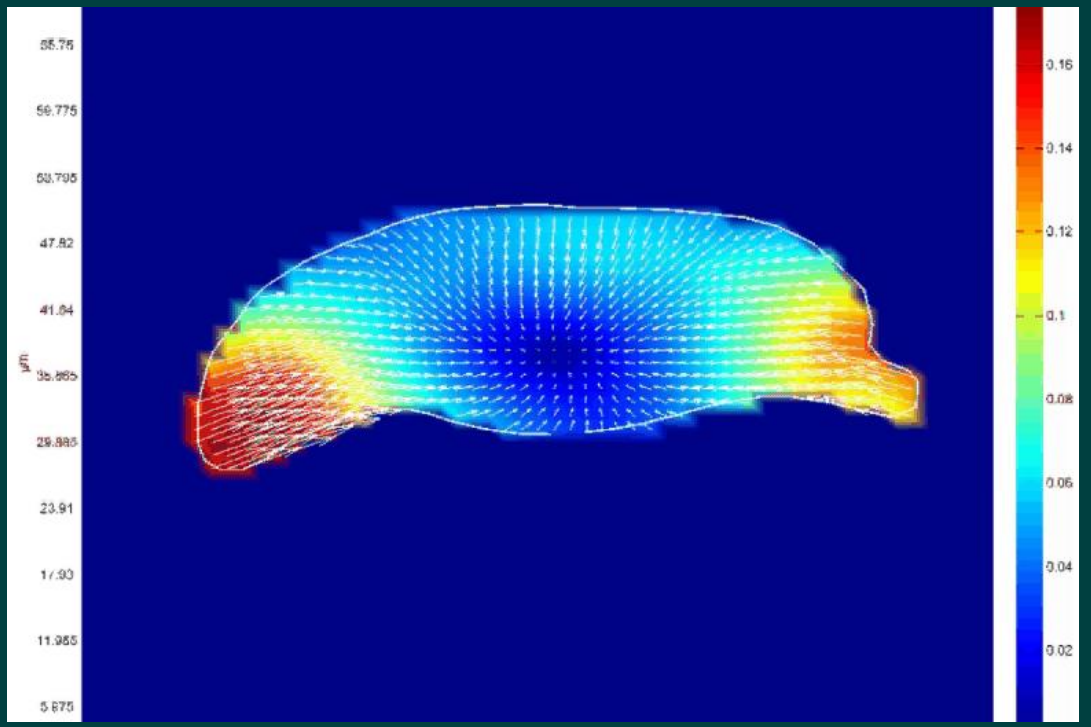


deformation map



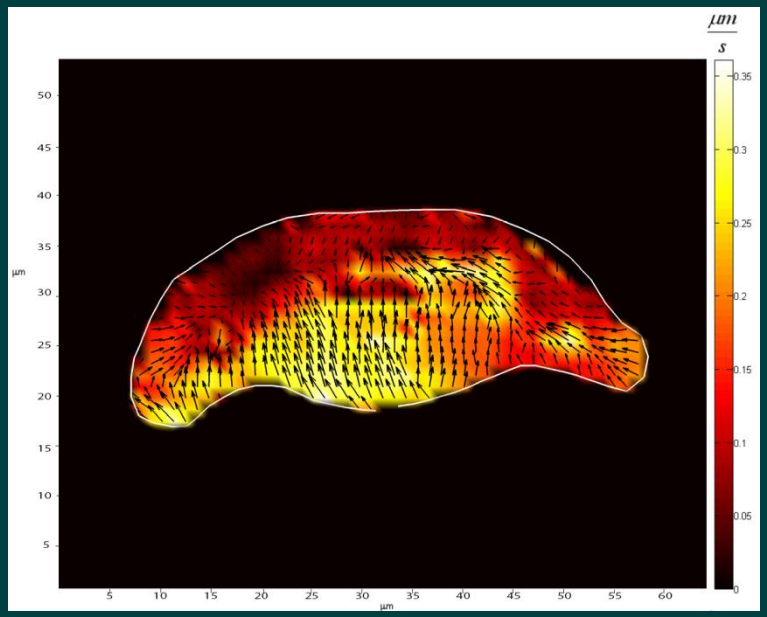
stress map

kPa

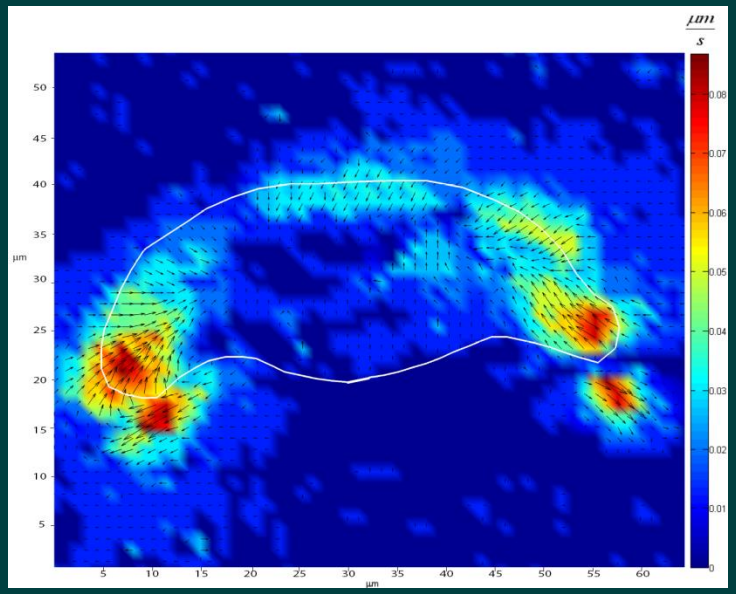


finite element-based approach
D. Ambrosi (Polytechnico di Torino)

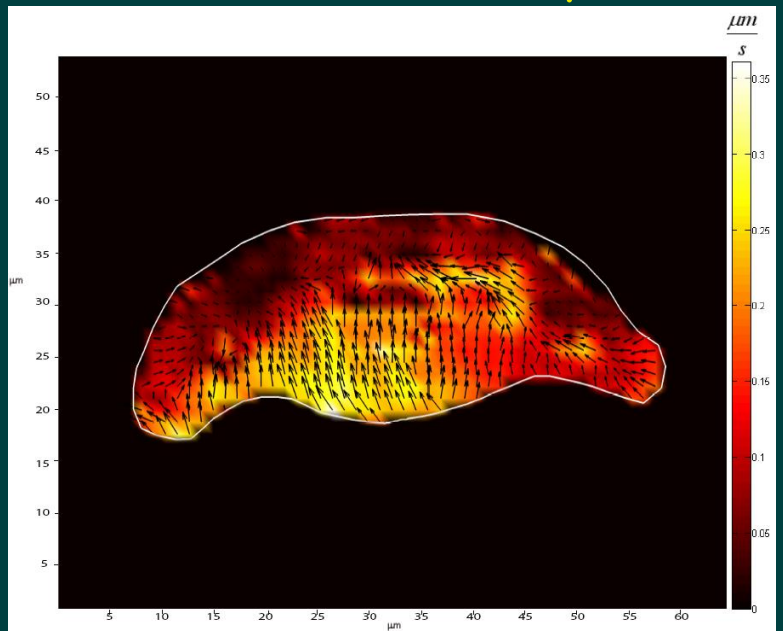
actin velocity



substrate velocity

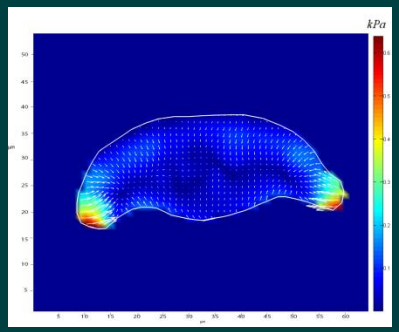


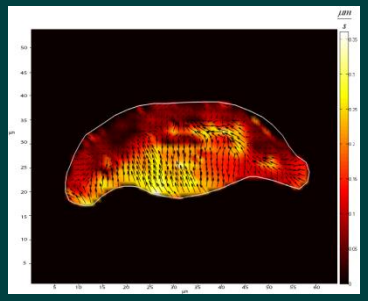
relative velocity



substrate/cytoskeleton viscous friction map

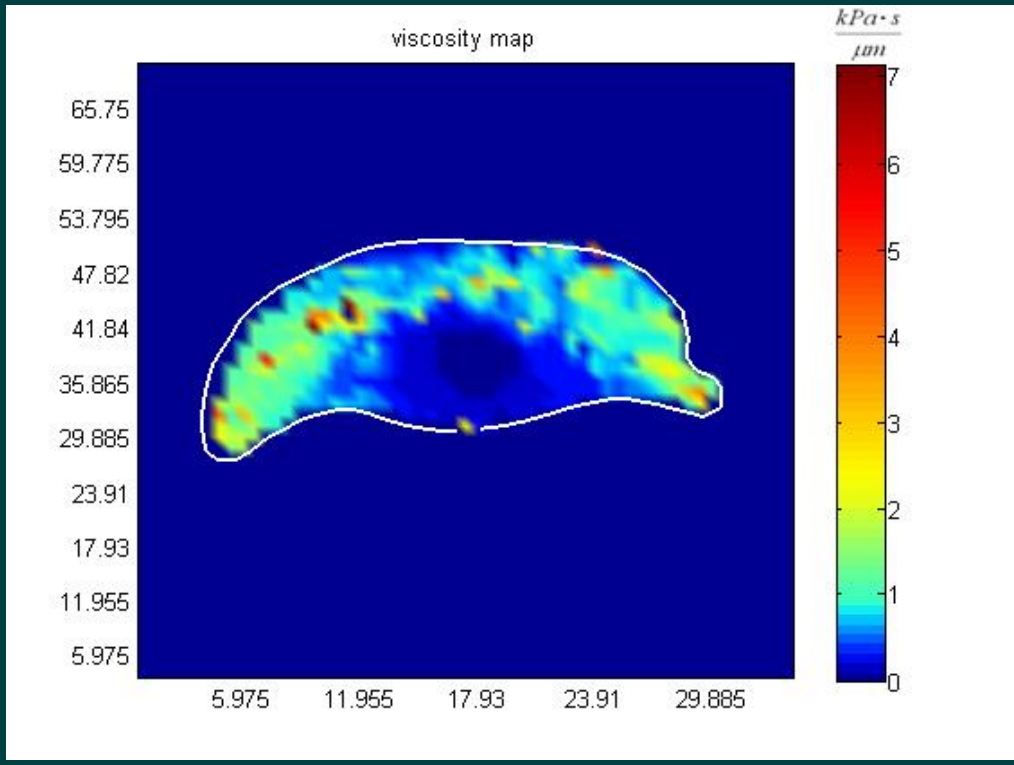
stress map



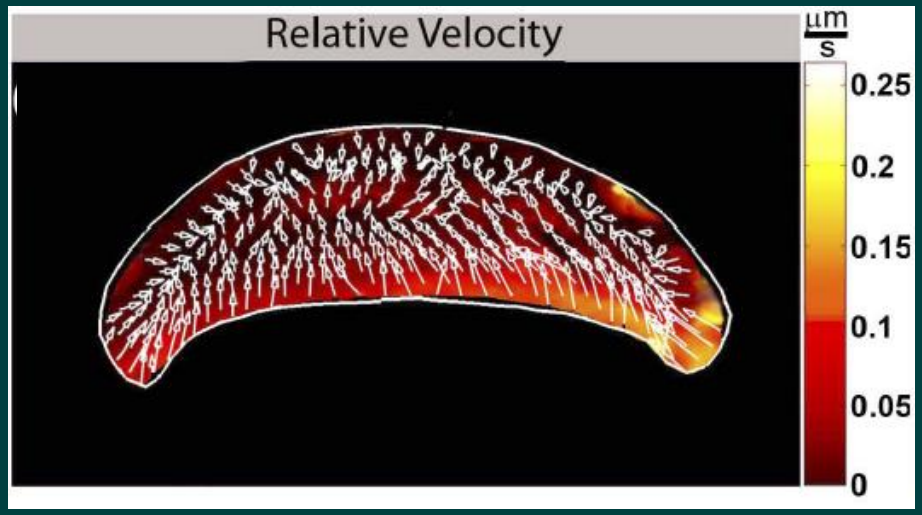


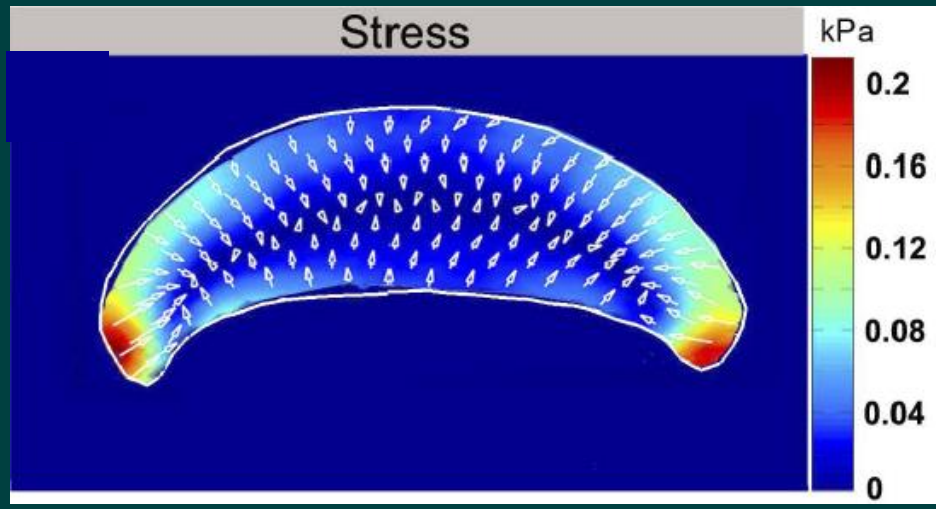
relative velocity map

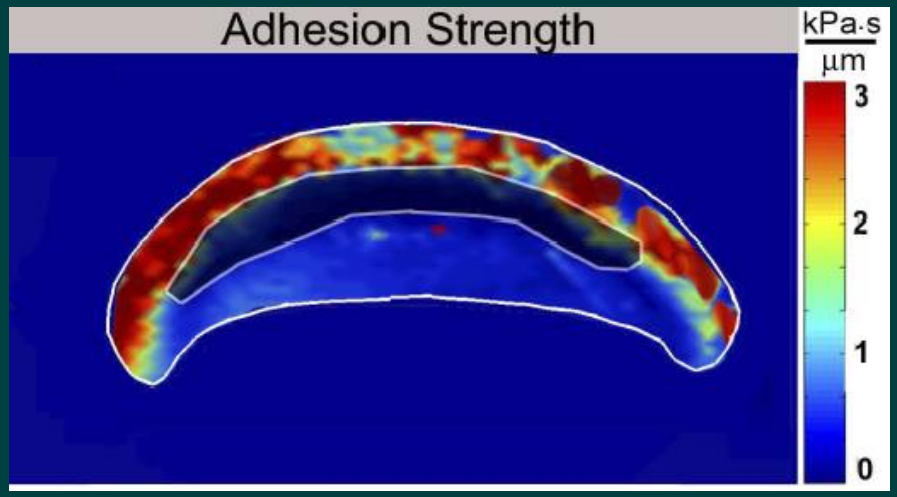
=

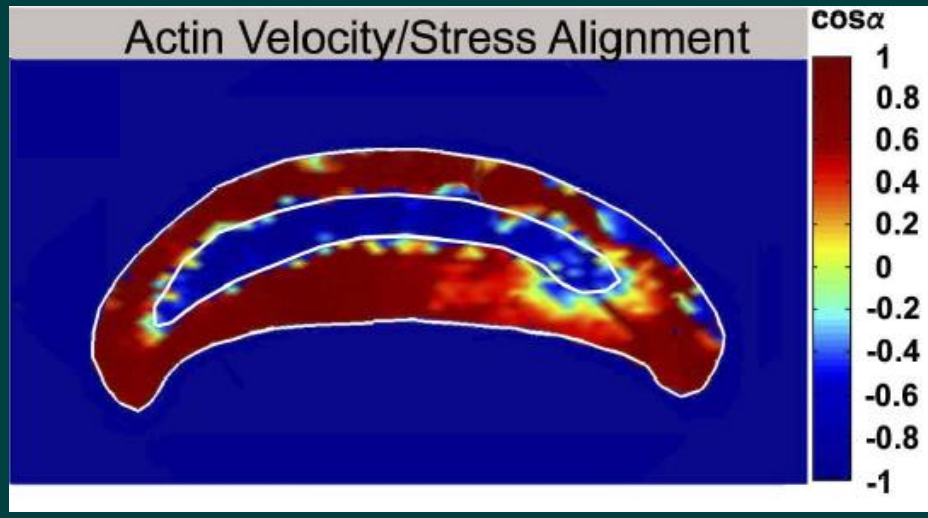


Problem with viscous description – stress is not always aligned with actin velocity

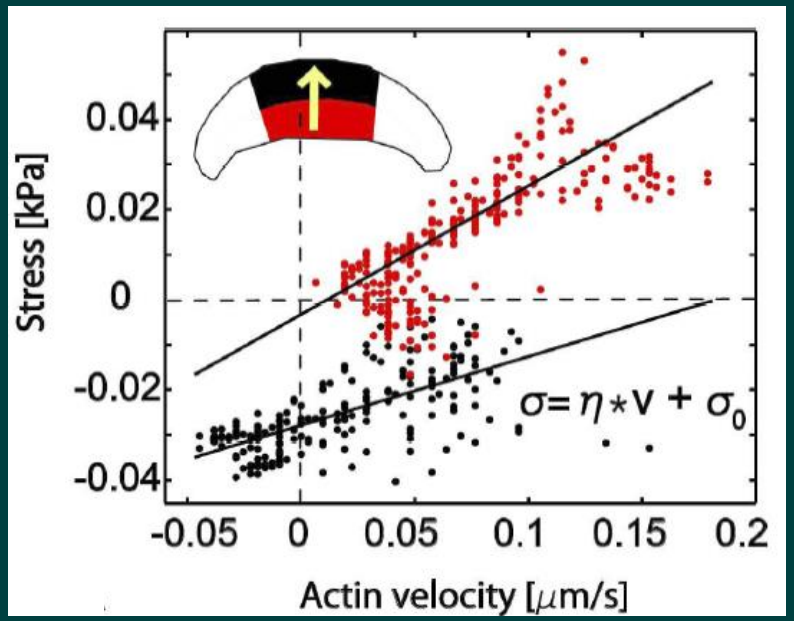


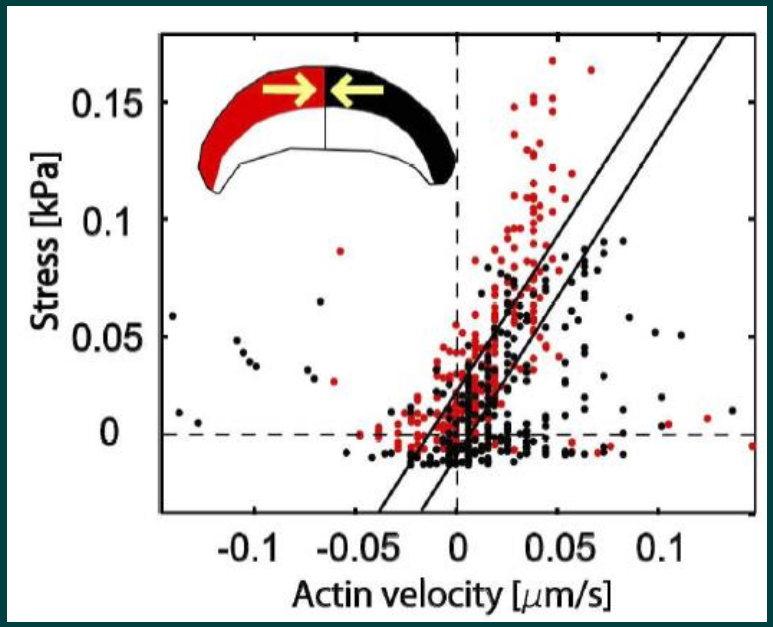


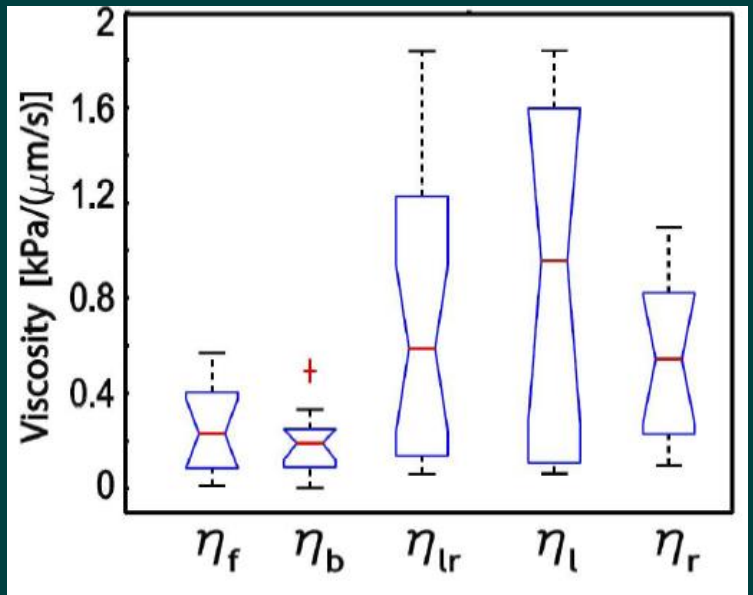


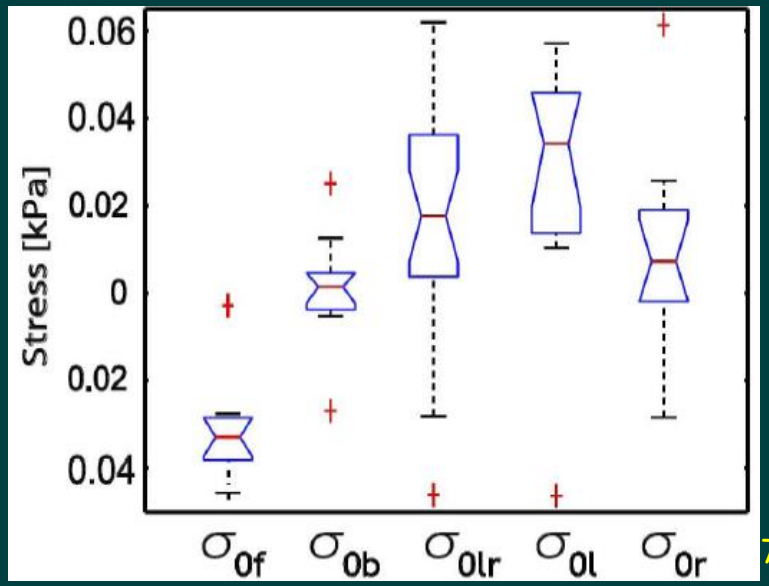


Stress vs actin velocity depending on direction and cell region









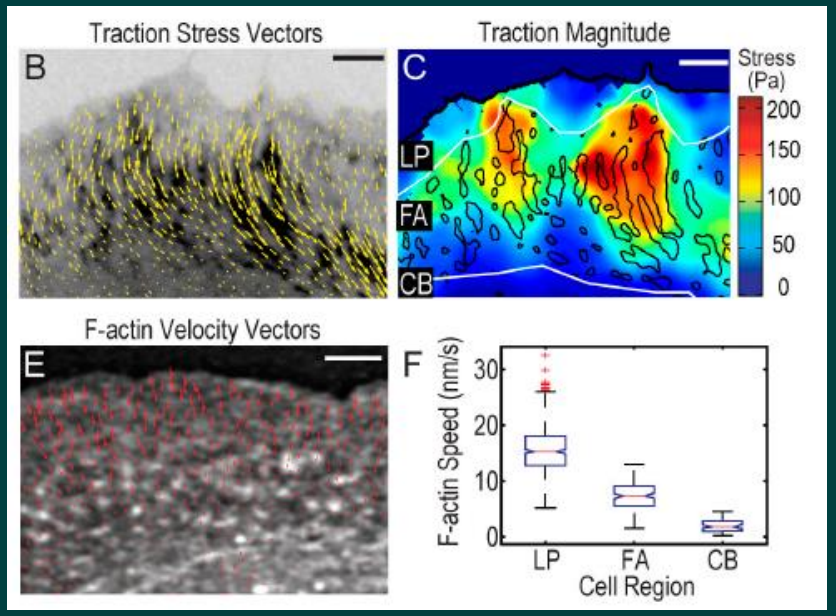
adhesions grip at the front, slip at the sides and back

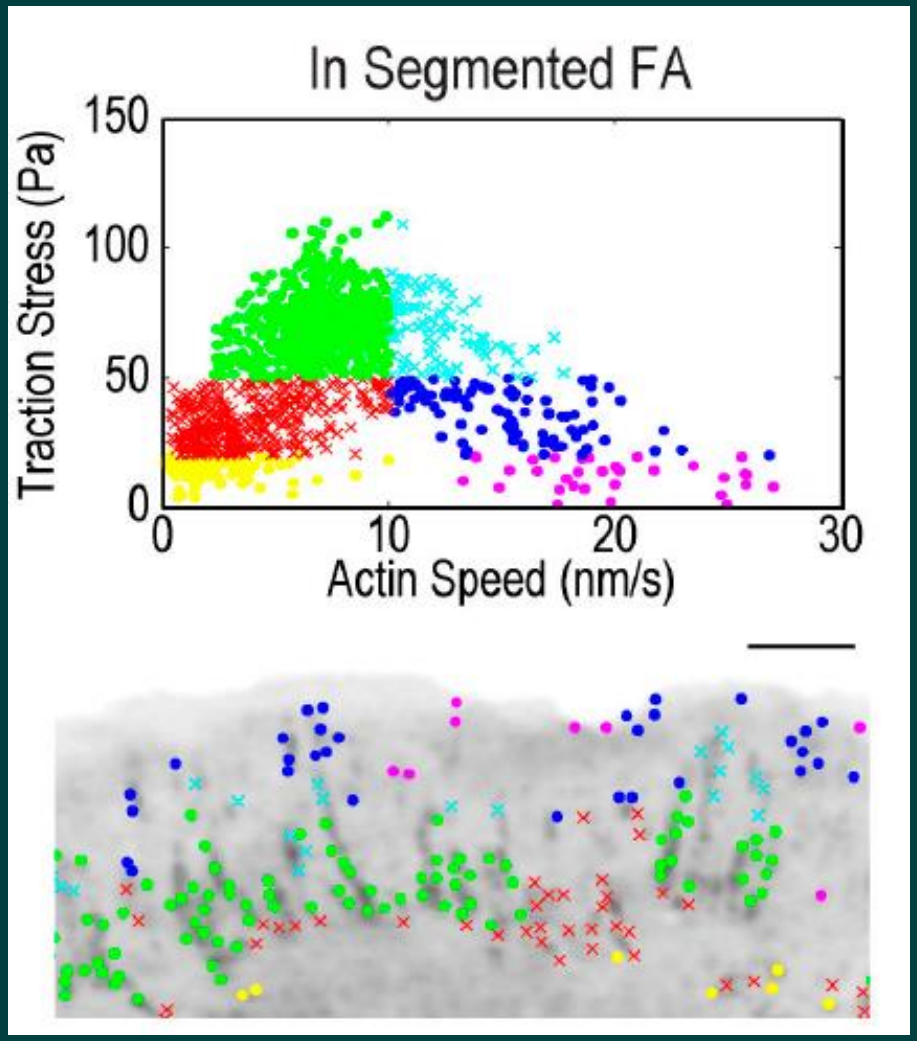
viscous friction at the sides is higher than at the back

- possible age-dependent adhesion mode switch, anisotropy

traction/velocity in epithelial cells: biphasic relation

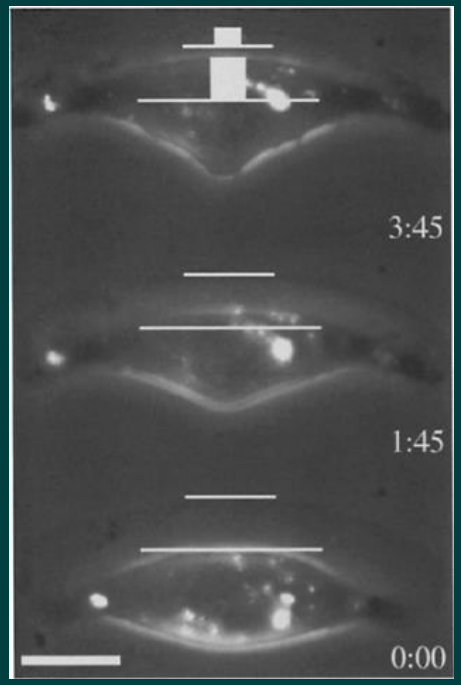
force decreases with velocity in lamellipodia, but increases with velocity in lamella



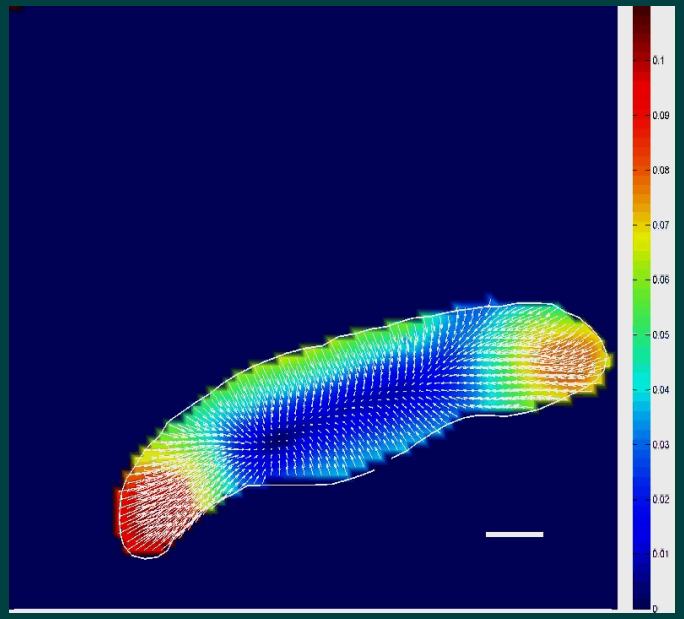


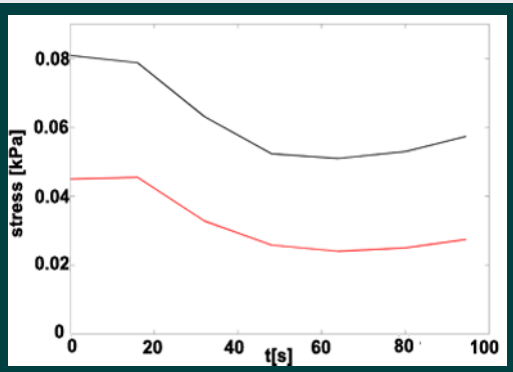
Gardel et al., 2008

What happens if actin assembly is inhibited (cytochalasin D)?



Leading edge stops, but the cell body continues to move for a while
(Anderson et al., 1996)





Significant part of the traction stress remains
(Fournier et al., 2010)

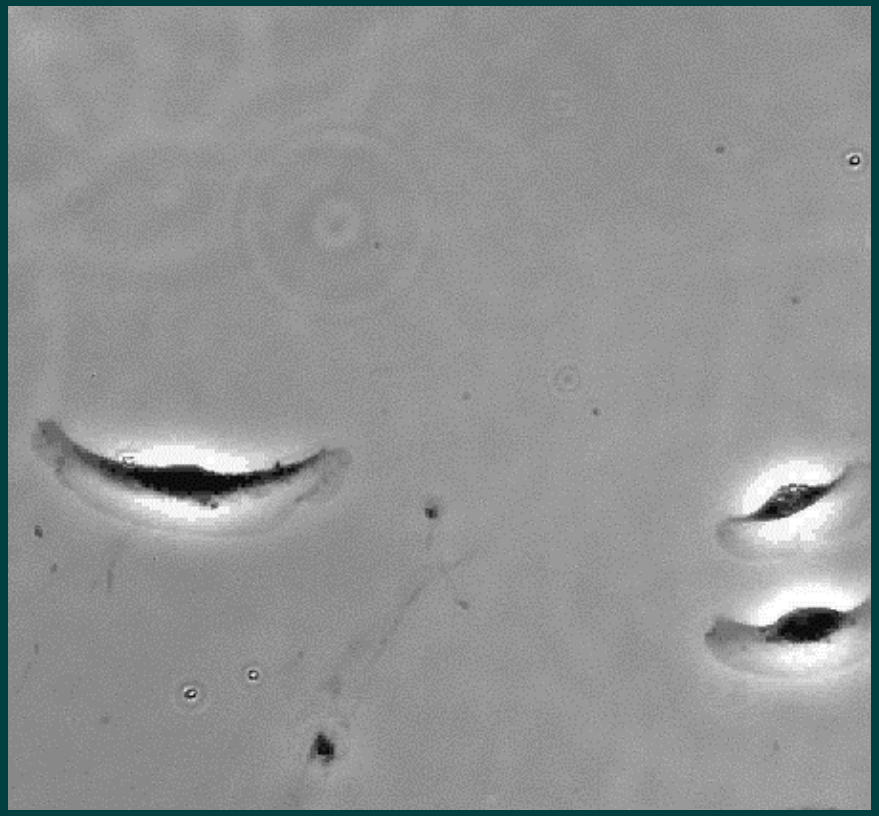
Actin assembly

-essential for cell motion

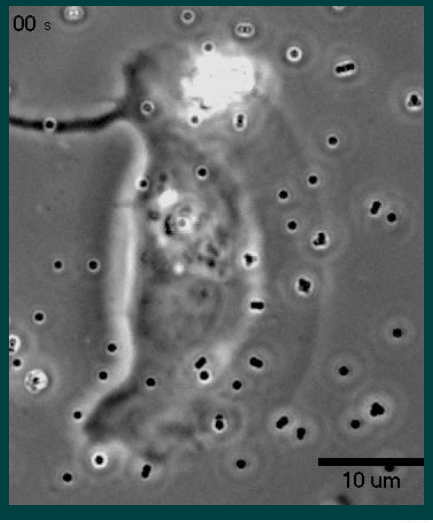
-does not produce a lot of force (?)

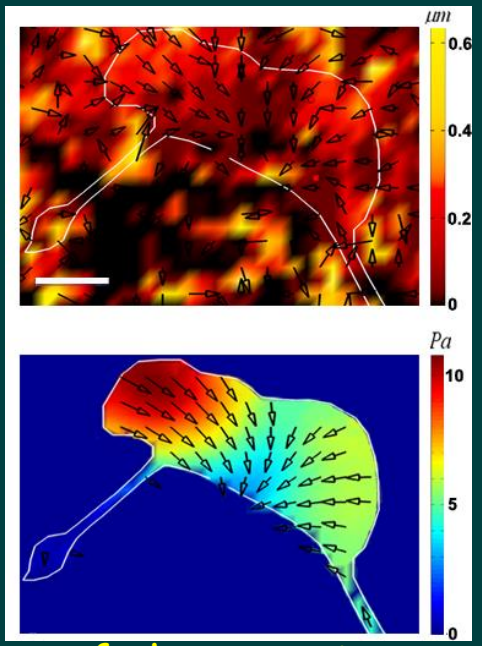
-traction stress and cell body motion are largely independent of actin assembly

when myosin II activity is inhibited (blebbisatin)



cell continues to move, but splits into fragments (Schaub et al., 2007)





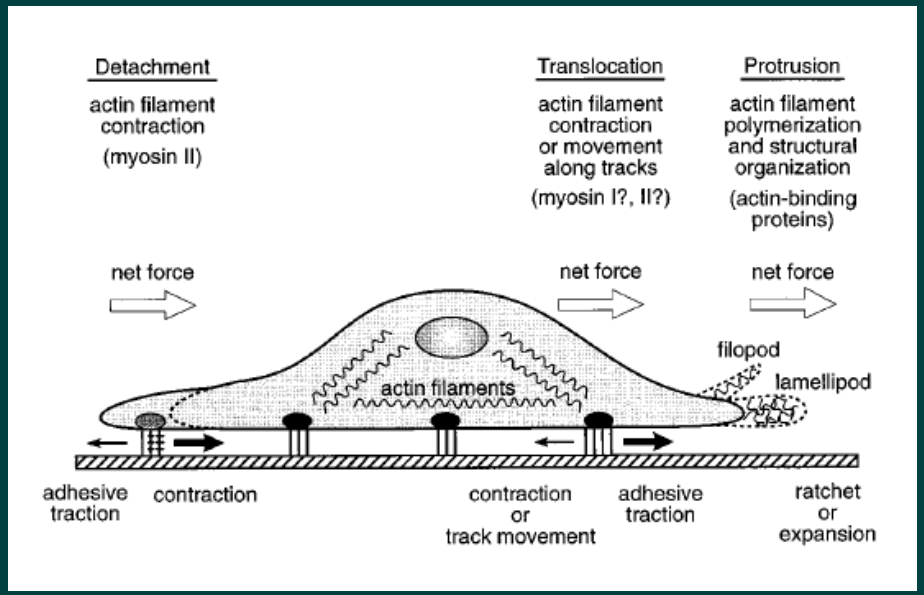
Most of the traction stress disappears (Fournier et al., 2010)

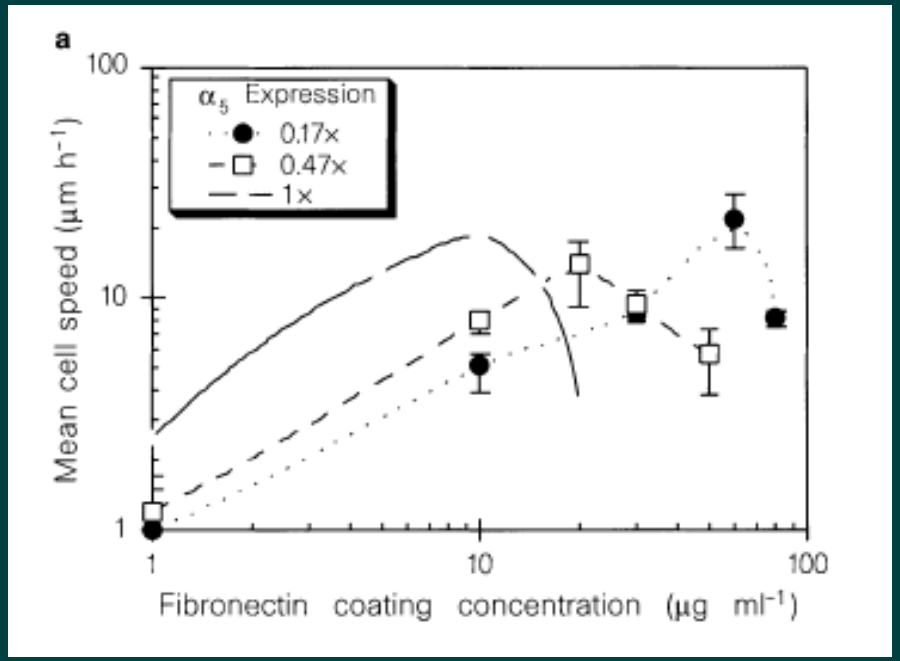
Myosin II activity

-essential for traction stress

-non-essential for cell motion

migration efficiency depends on the adhesion strength: intermediate strength is optimal





varied concentrations of adhesive molecules in the cell and ligands on the substrate

Lauffenburger and Horwitz, Cell, 1996

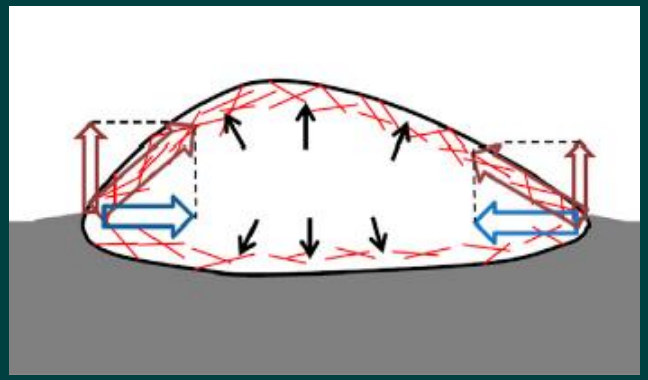
Palecek et al., Nature, 1997

typical traction stress 100 Pa
typical cell area 1000 μm
range of forces 100 nN

less the 1 pN is needed to overcome viscosity from the liquid medium

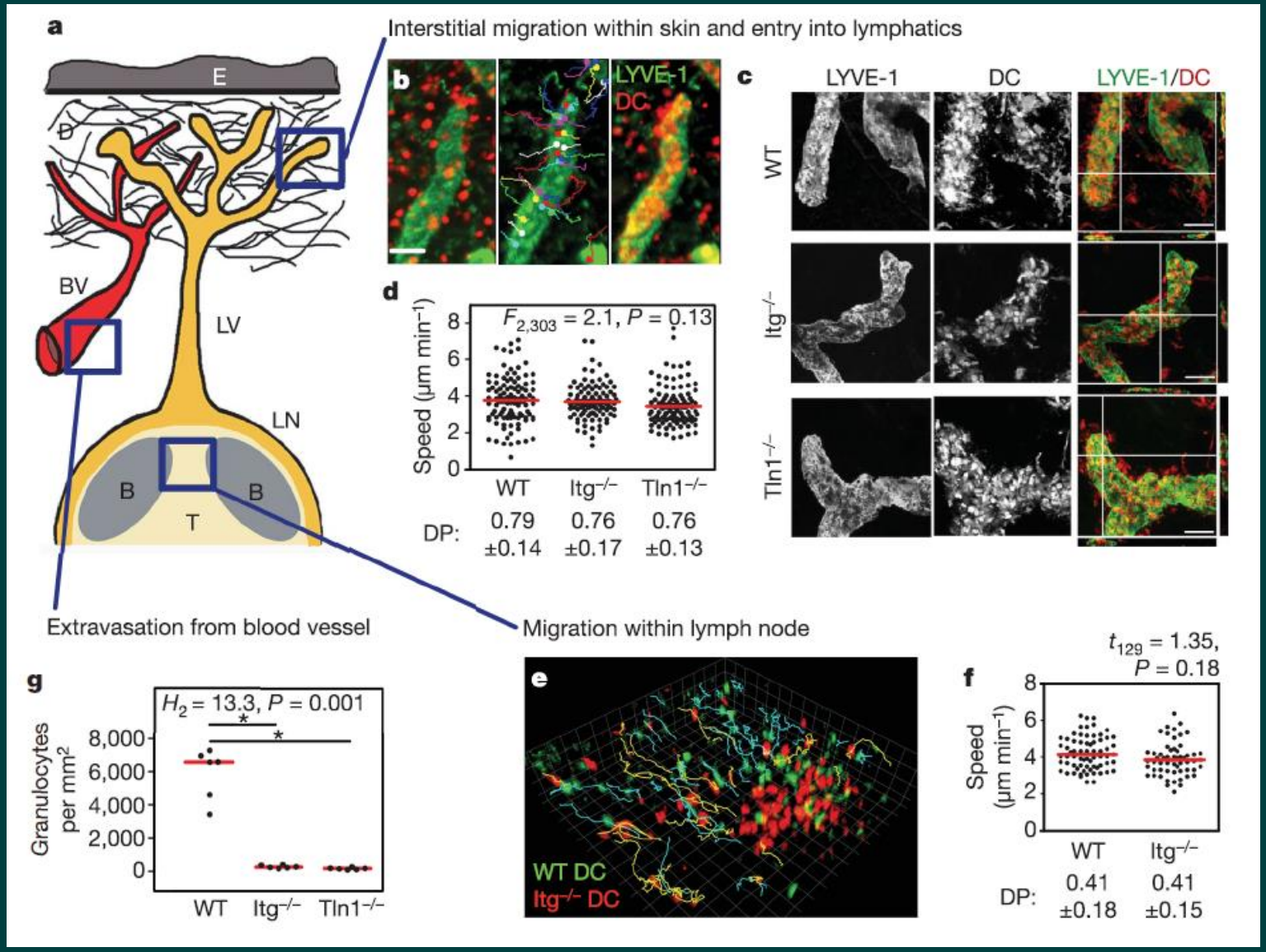
thus, the cells are applying force mostly to overcome their own adhesion

mostly pulling forces (except from under the middle of the cell) with zero sum



if adhesion strength is reduced it should be possible to move with less force

migration without specific adhesion (integrin-null cells)

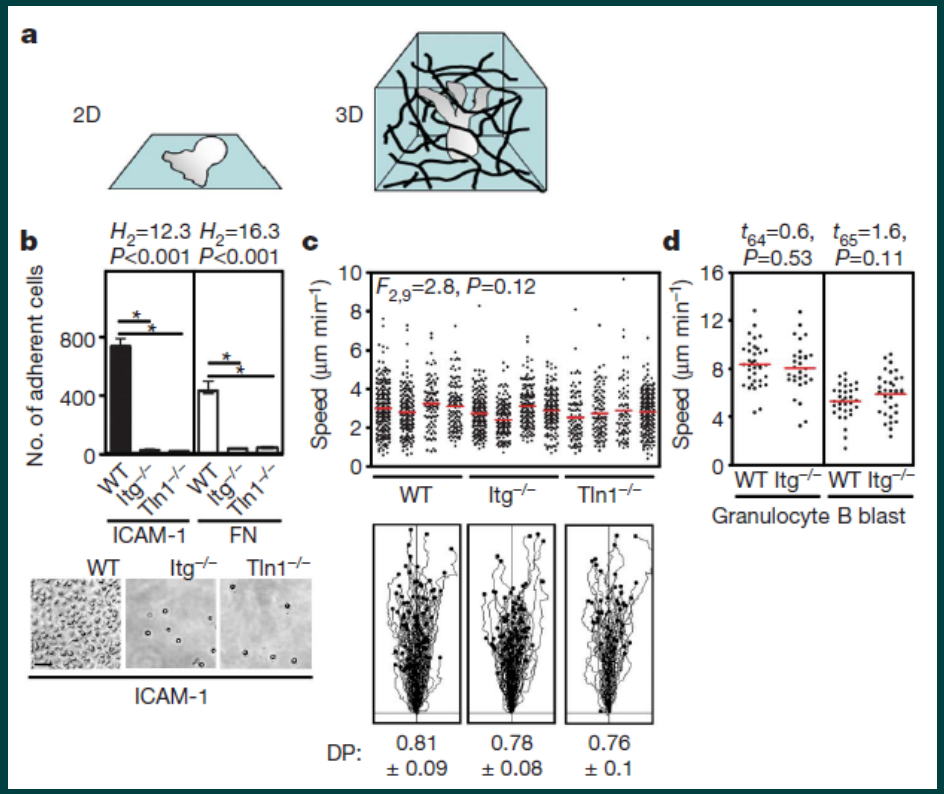


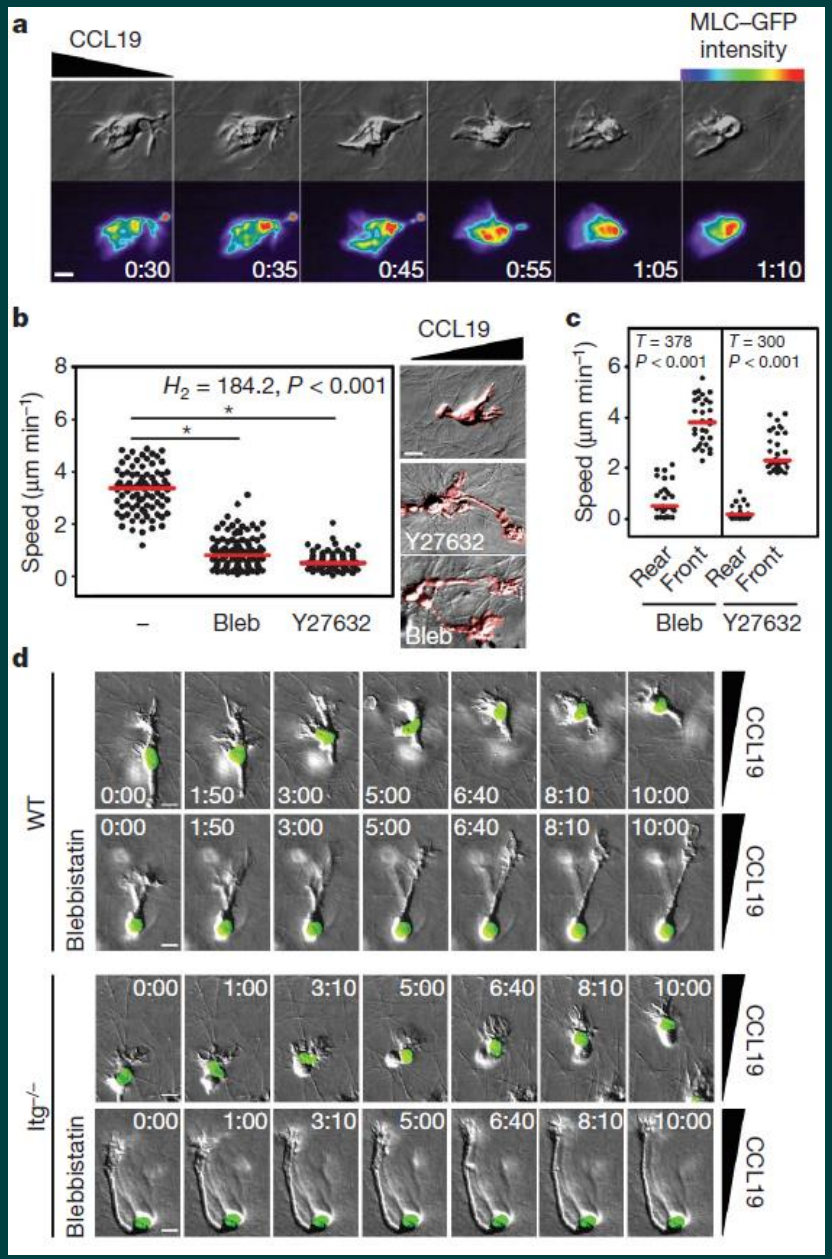
leucocytes without adhesion move well in the lymph nodes and skin, but cannot enter the blood vessels

Lammermann et al., 2008

in vitro in 3D gel

myosin is required for migration in 3D

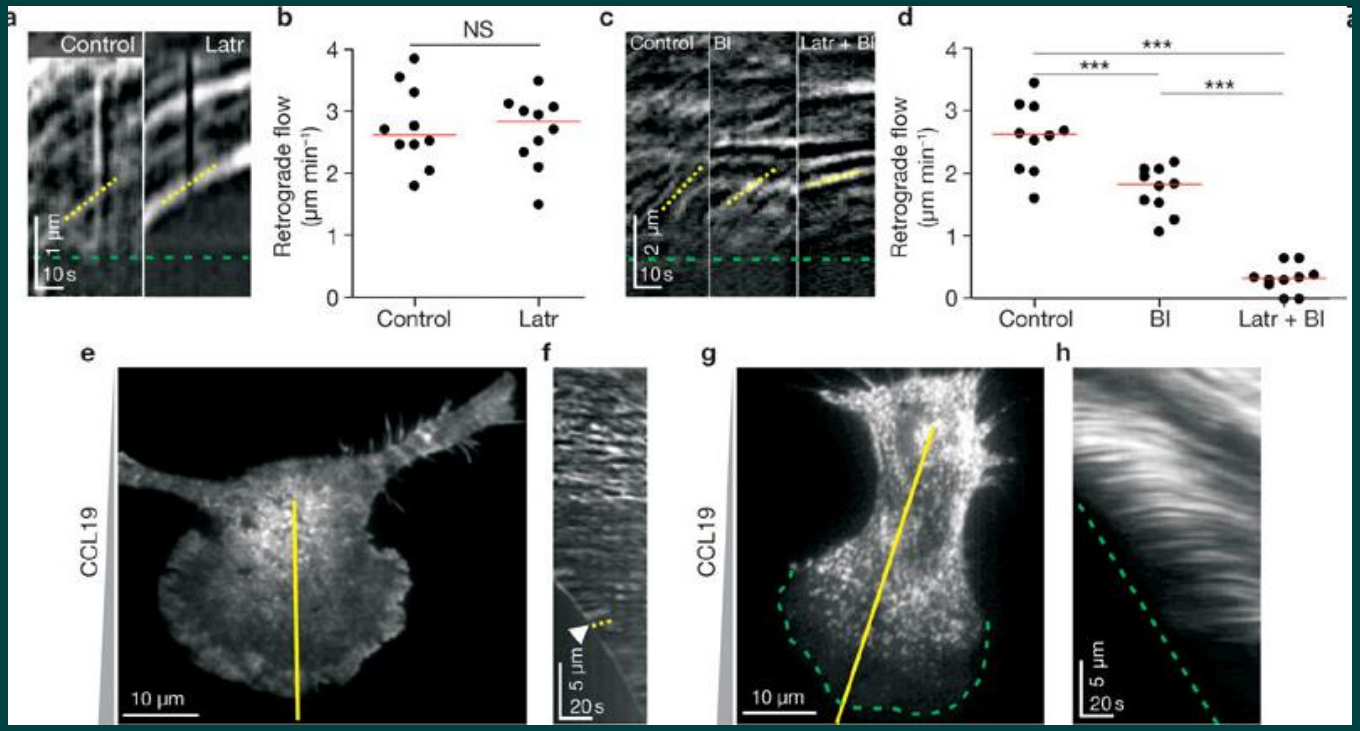




adhesion-free cells do not stick to the surface but migrate well in 3D gel

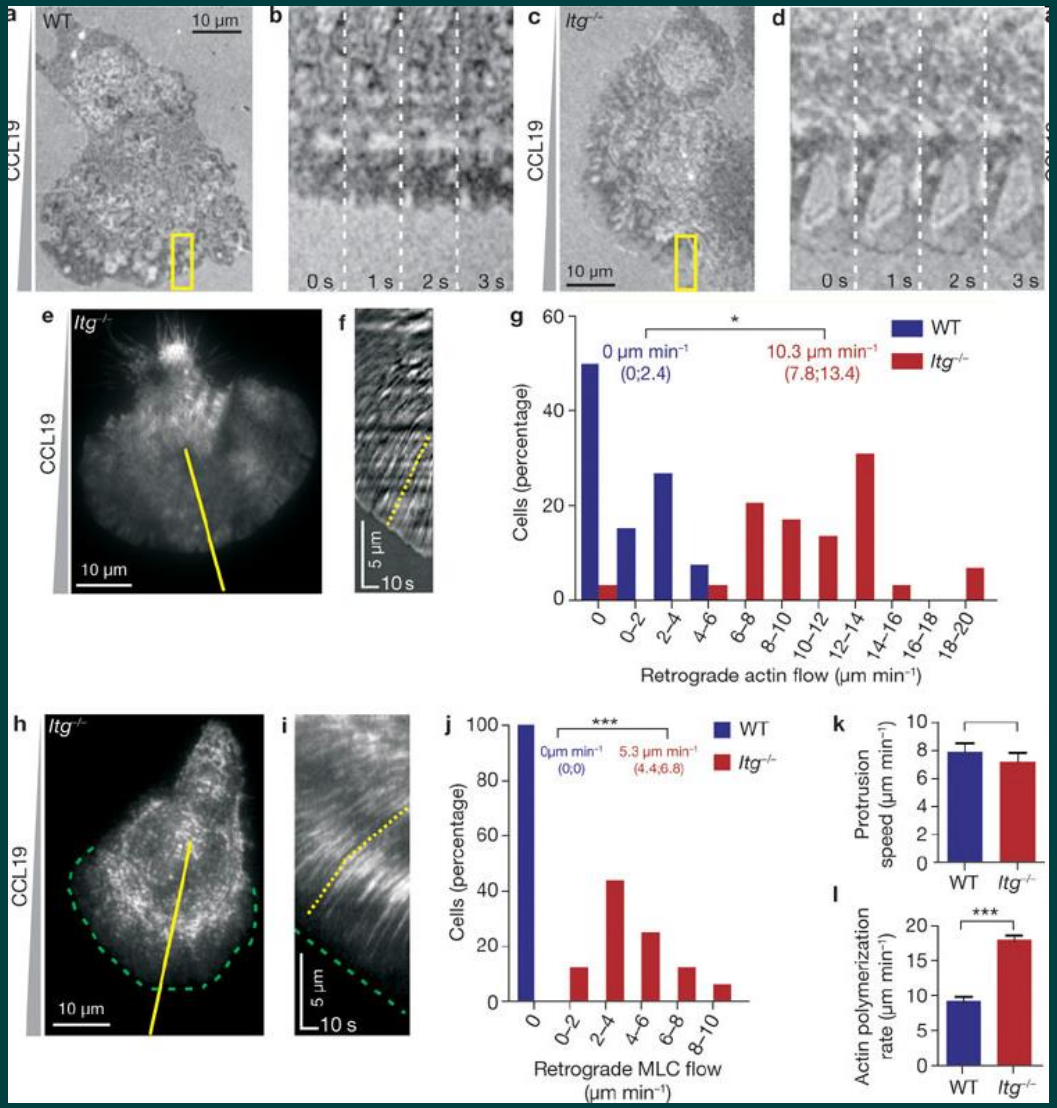
What is actin flow dynamics in adhesion-independent cells?

retrograde actin flow is slow on adhesive surfaces



Renkawitz et al., Nature Cell Biology, 2009

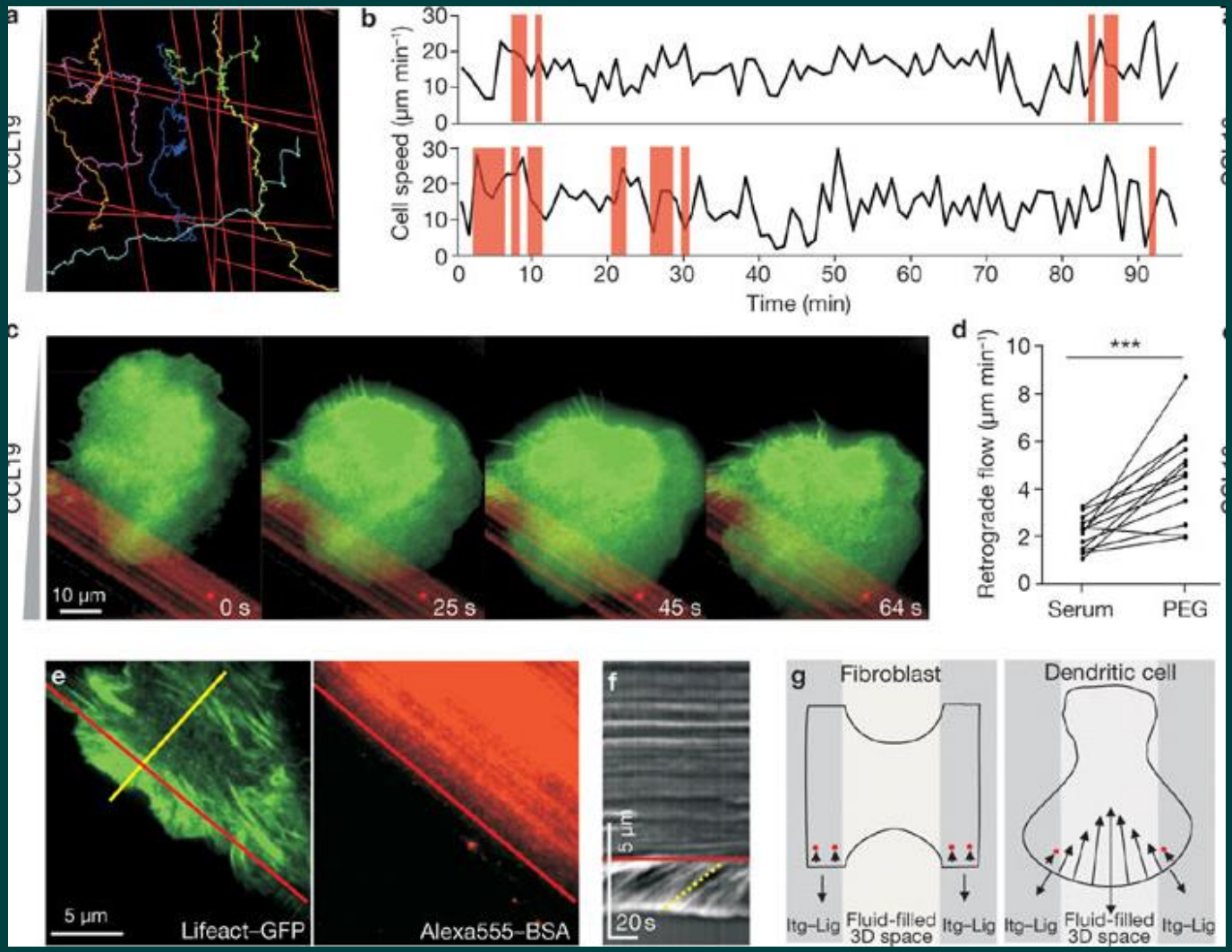
Retrograde flow and actin polymerization rate increase in the absence of adhesion, so that protrusion rate remains high



observation in the chamber between two surfaces

Renkawitz et al., Nature Cell Biology, 2009

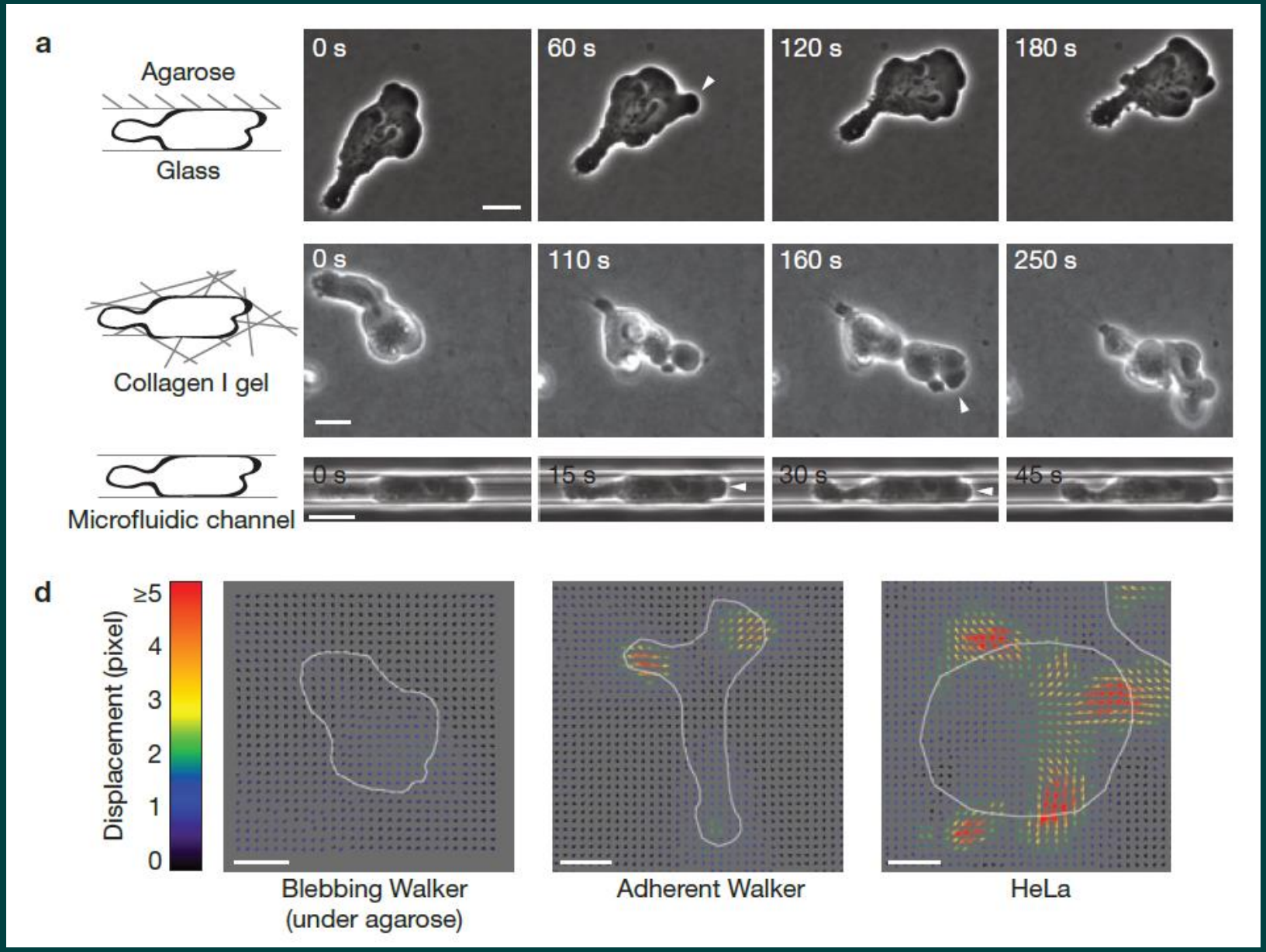
leucocytes, unlike fibroblasts, move equally well with and without adhesion



dynamics at the transition between adhesive and non-adhesive surfaces

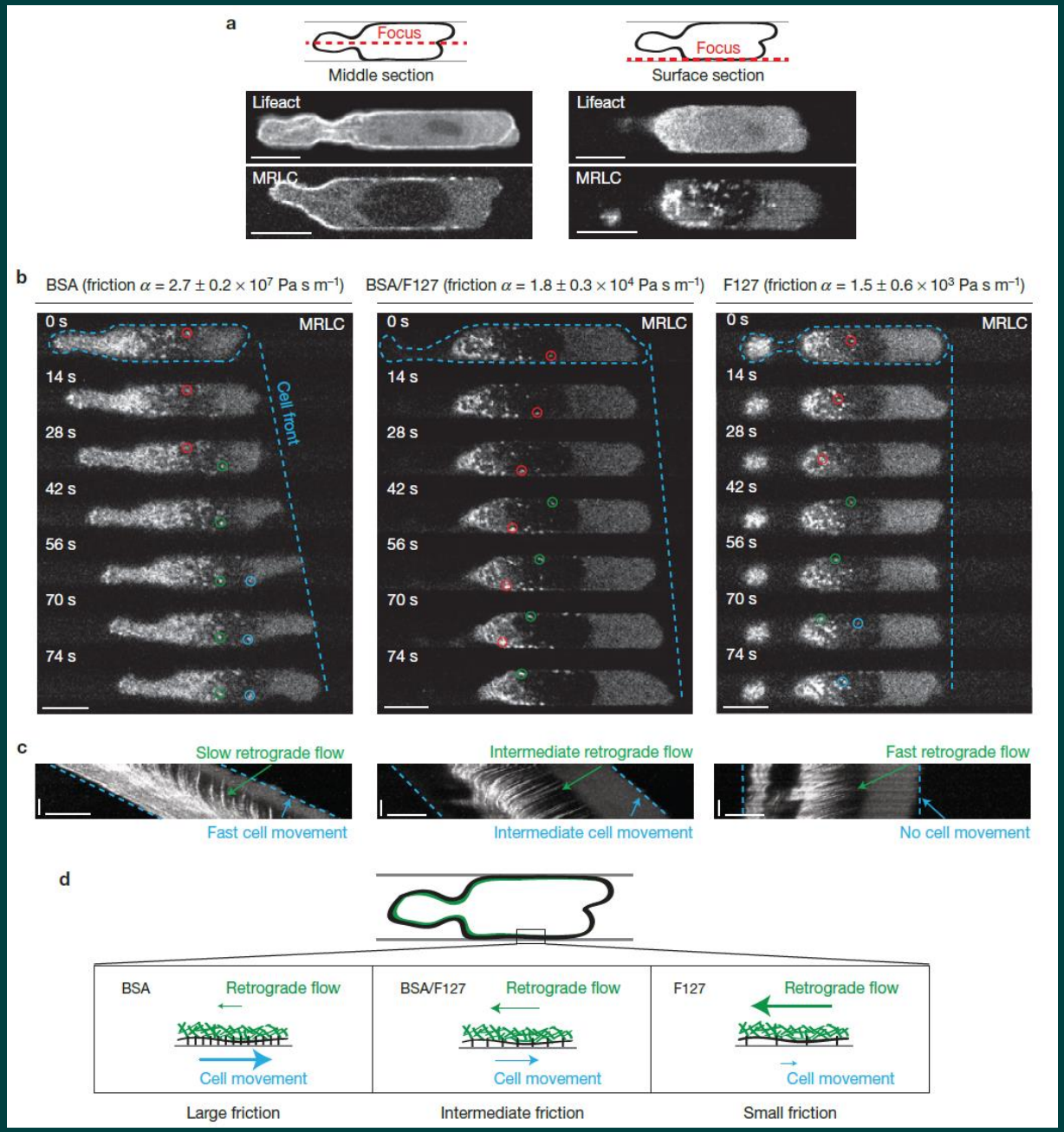
Renkawitz et al., Nature Cell Biology, 2009

Adhesion-independent force transmission



Bergert et al., 2015

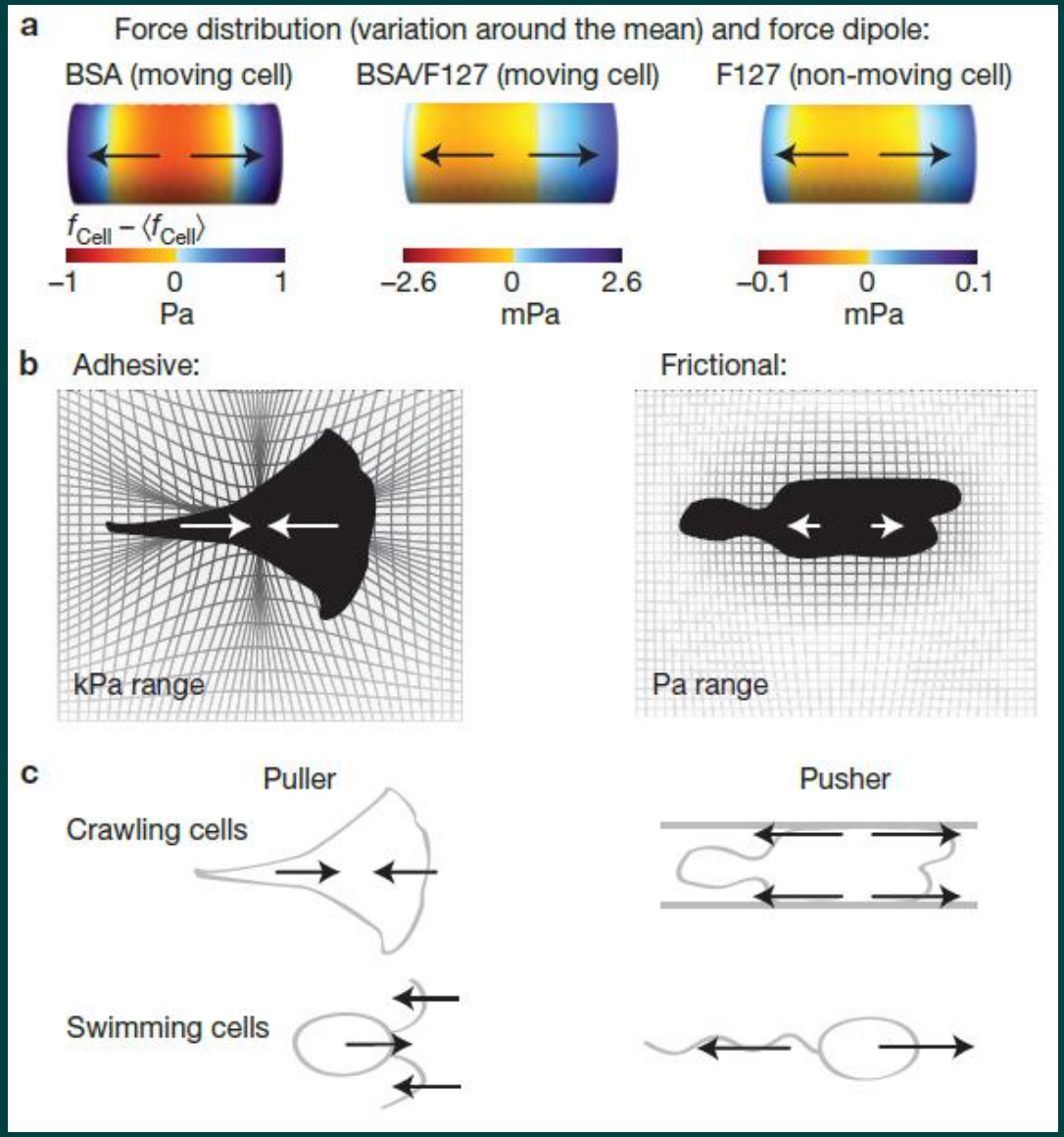
Friction is required for motion even without specific adhesion



motion velocity depends on surface friction

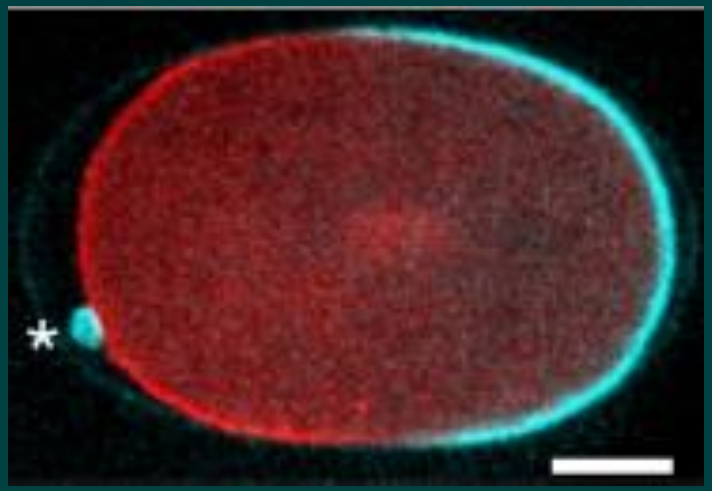
Bergert et al., 2015

Non-adhesive cells are pushers

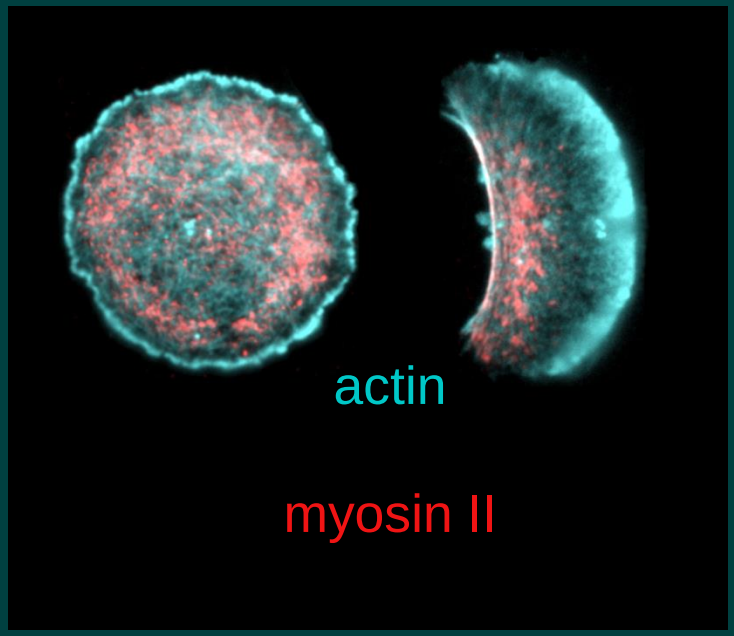


Bergert et al., 2015

mechanisms of polarization



Asymmetric fertilized oocyte
of C. elegans
(PAR proteins)



Motile cell fragment

examples of biological patterns at different scales

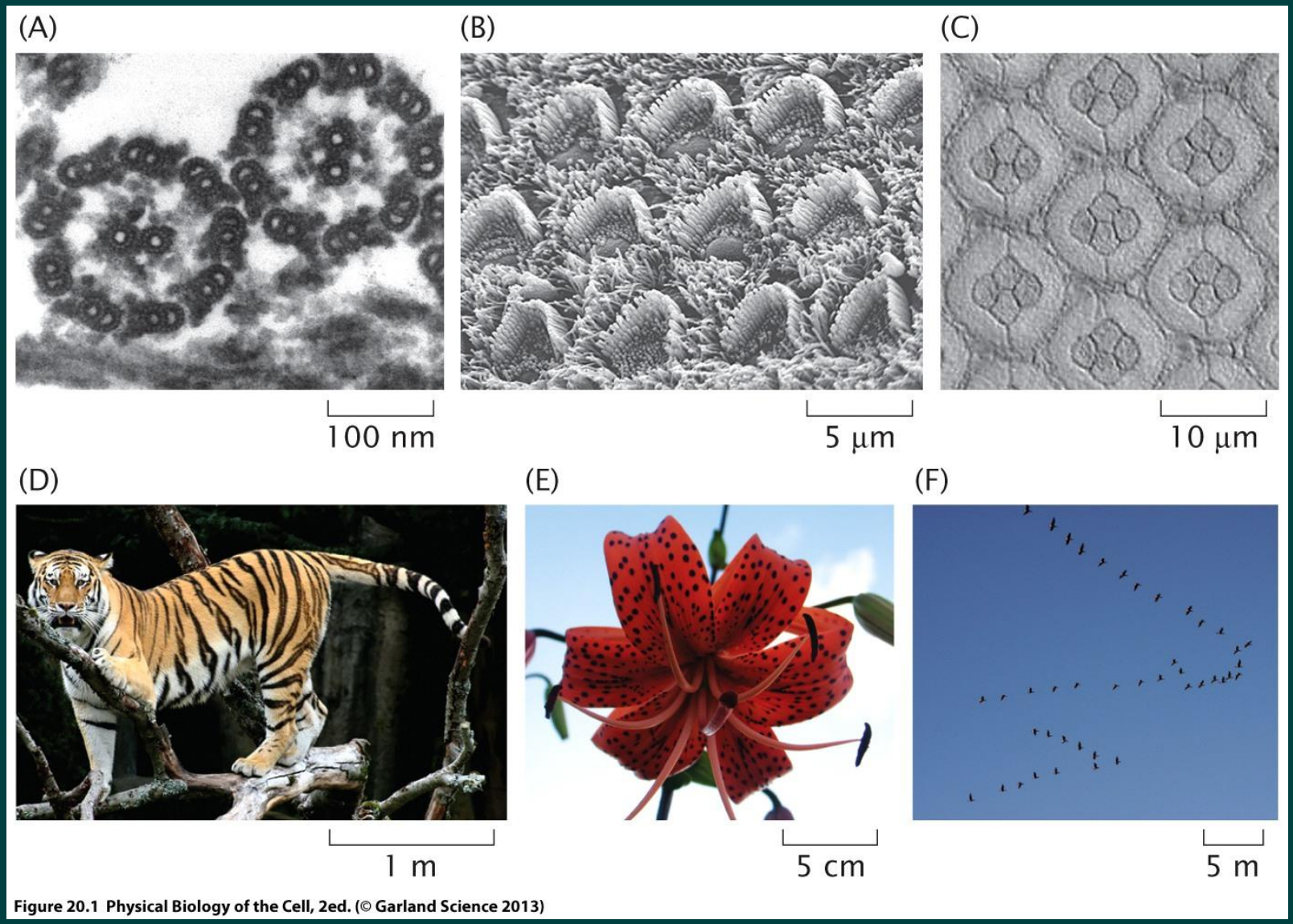
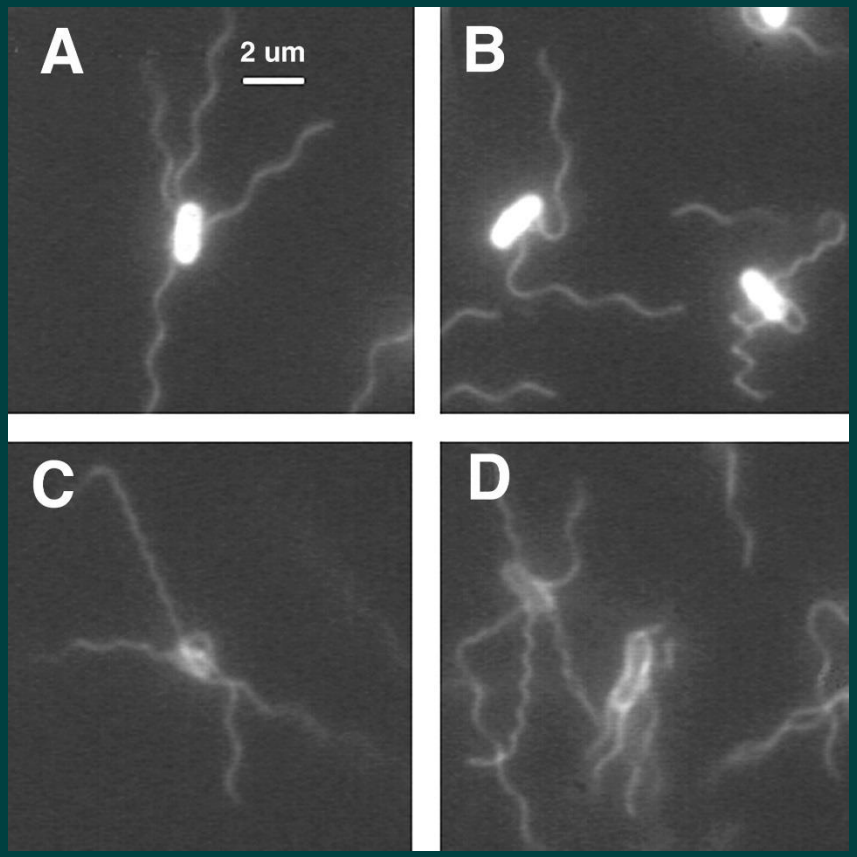
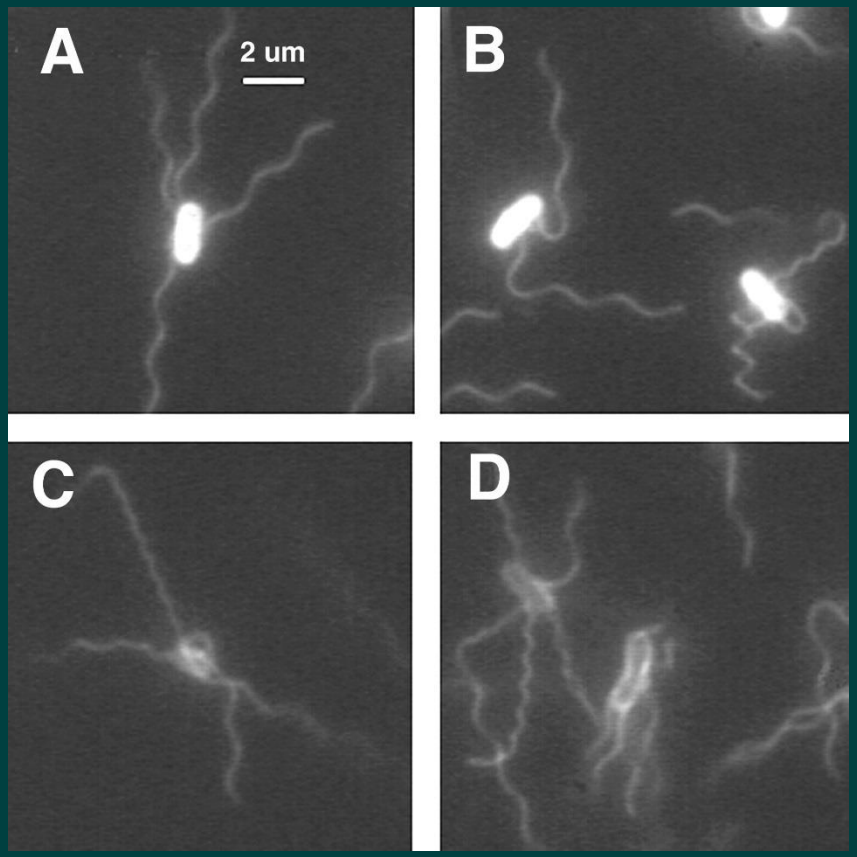


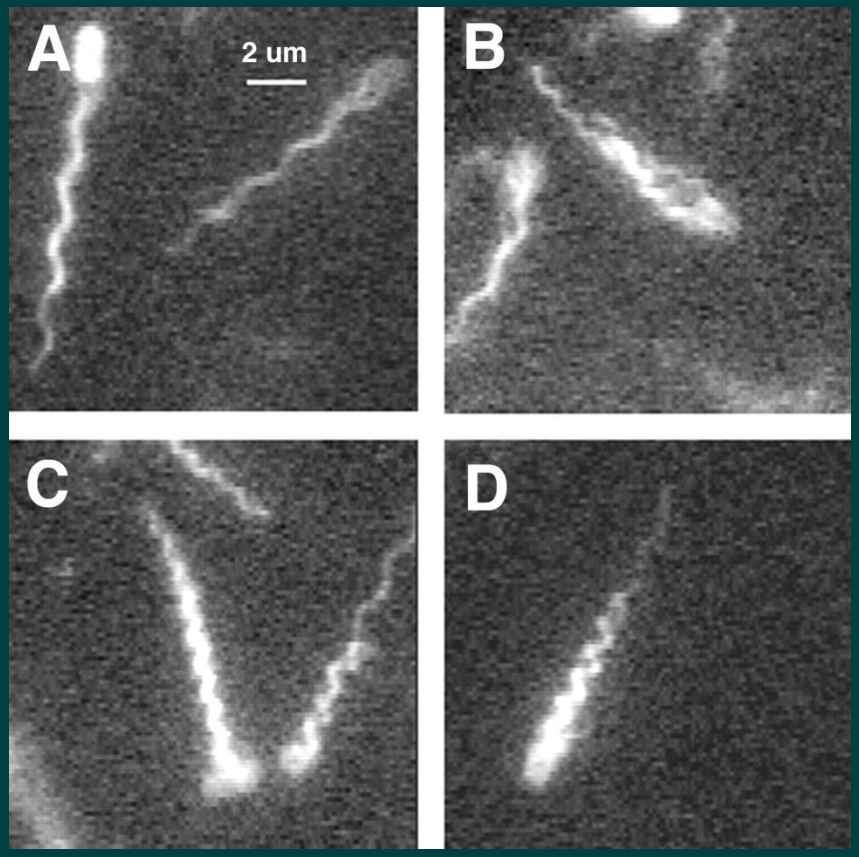
Figure 20.1 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

How is directionality achieved in simple systems?

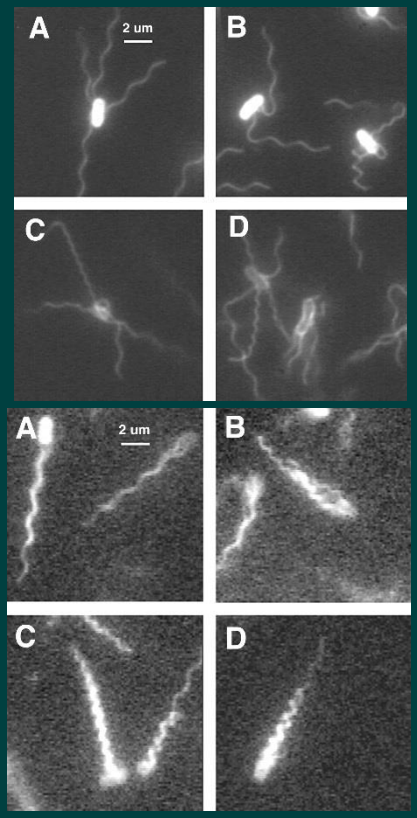


How is directionality achieved in simple systems?



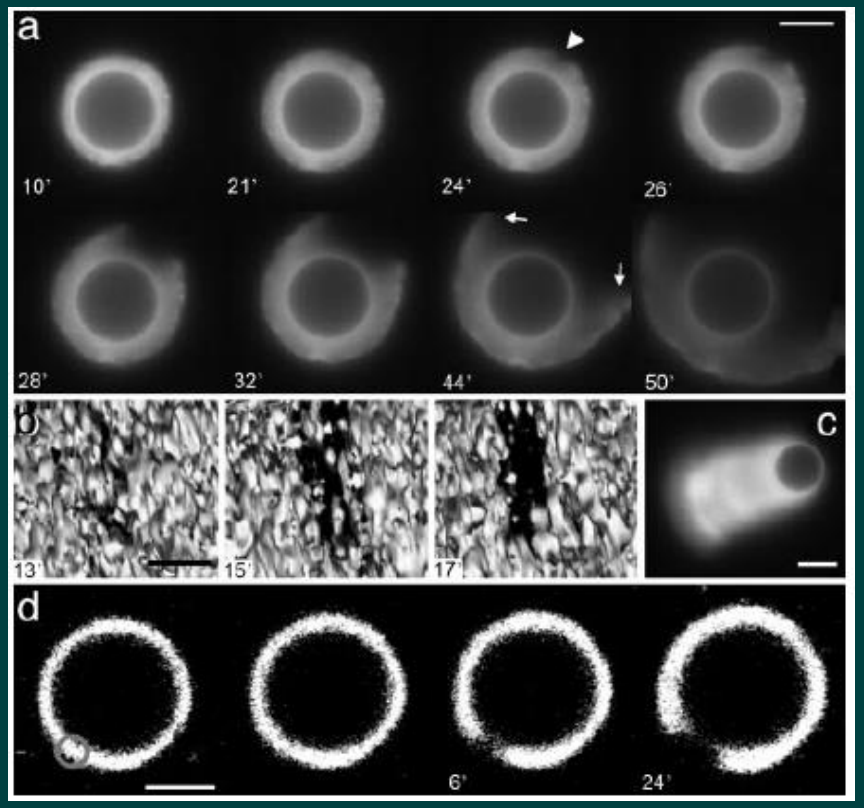


How is directionality achieved in simple systems?



Multiple flagella form
a single bundle in bacteria

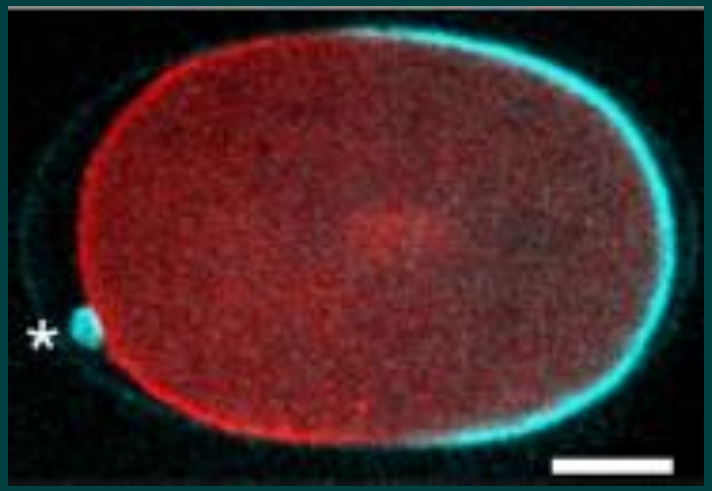
(Howard Berg lab)



Actin shell around bead breaks in a unique site

(Van der Gucht et al., 2005)

mechanisms of polarization



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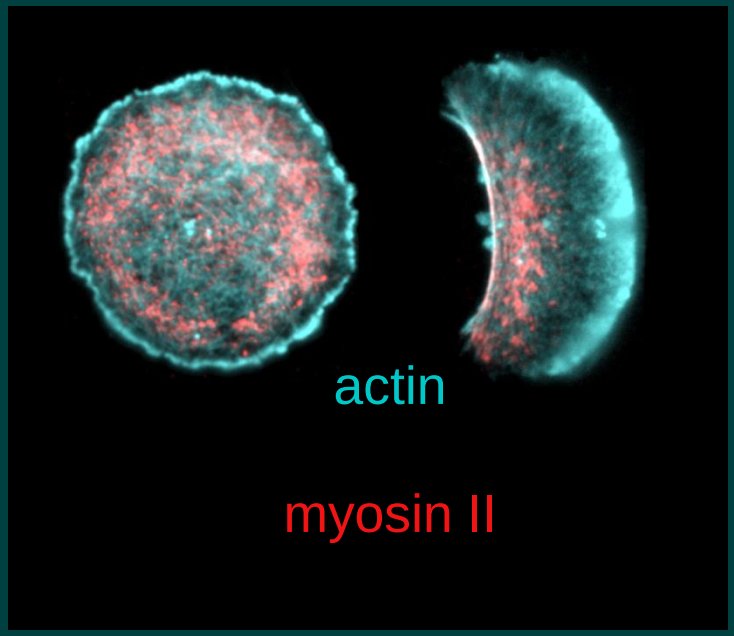


Motile cell fragment

How do millions of molecules spontaneously segregate against diffusion?

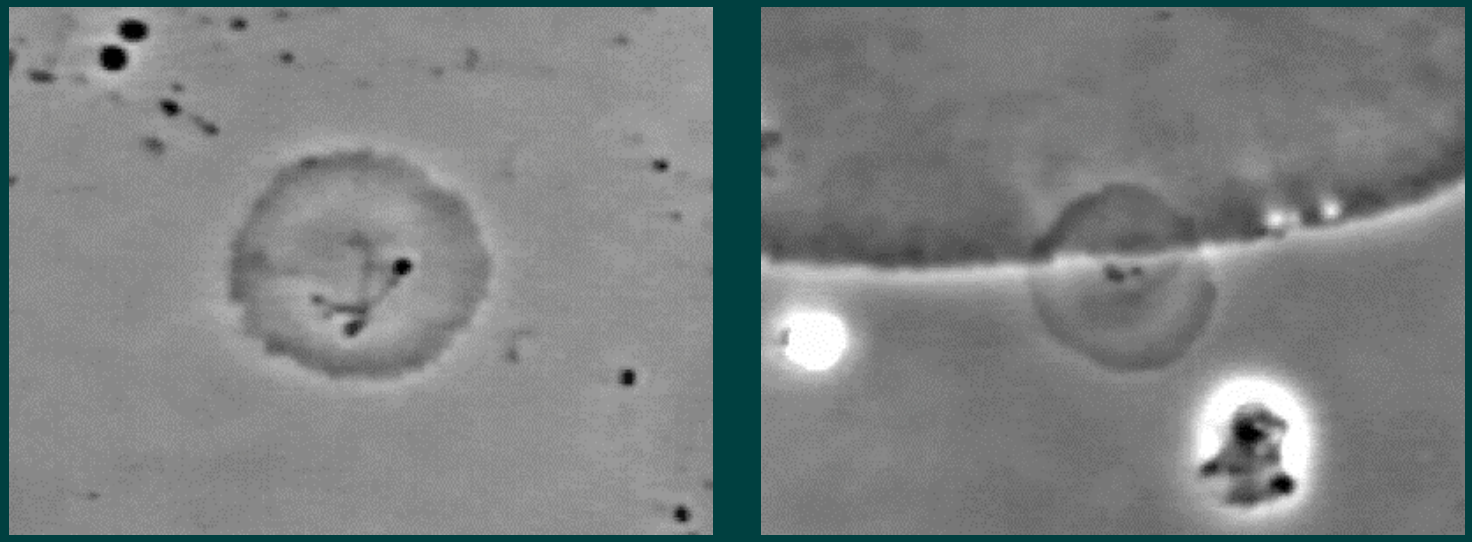
we will consider 3 types of mechanisms:

reaction-diffusion

mechanical feedback (from membrane and/or motion)

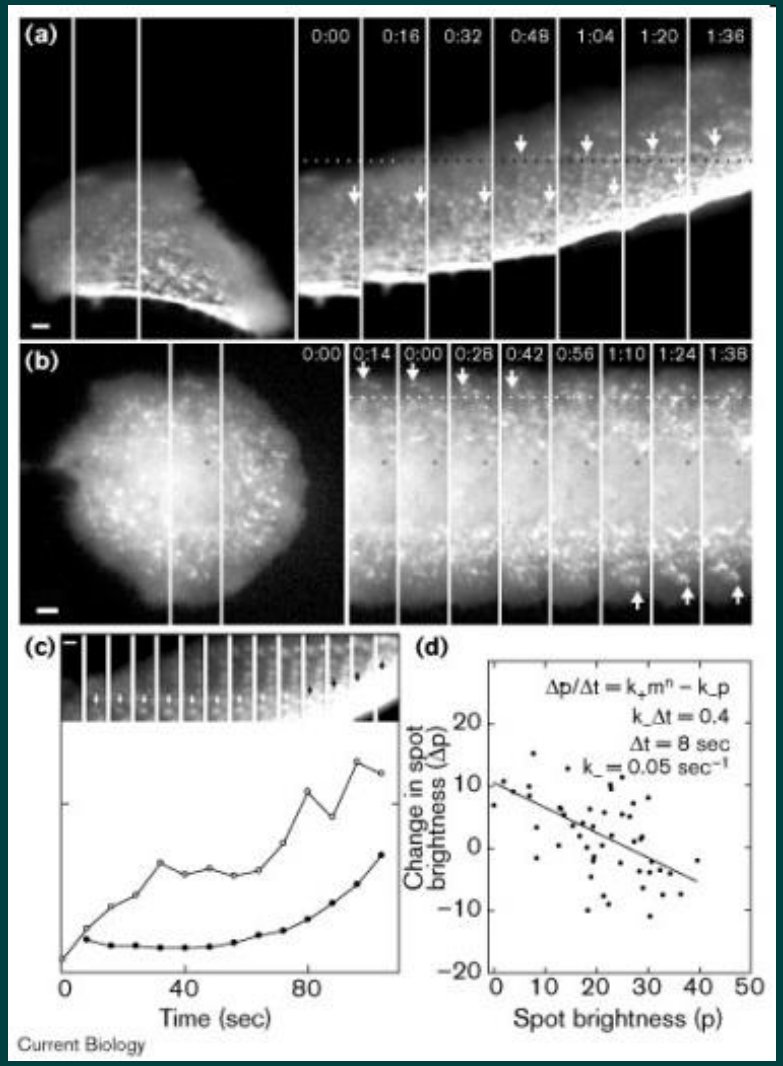
Ising-like mechanisms

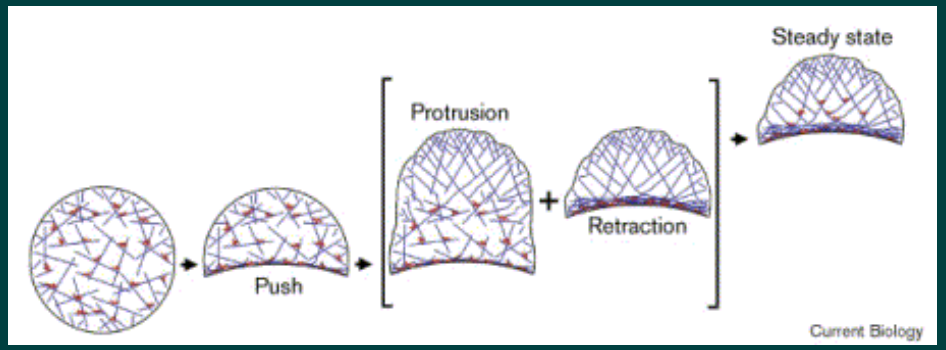
Positive feedback between motion and polarity



Verkhovsky et al., Curr. Biol., 1999

Polarization mechanisms:
mechanical – myosin II is swept to the back during motion

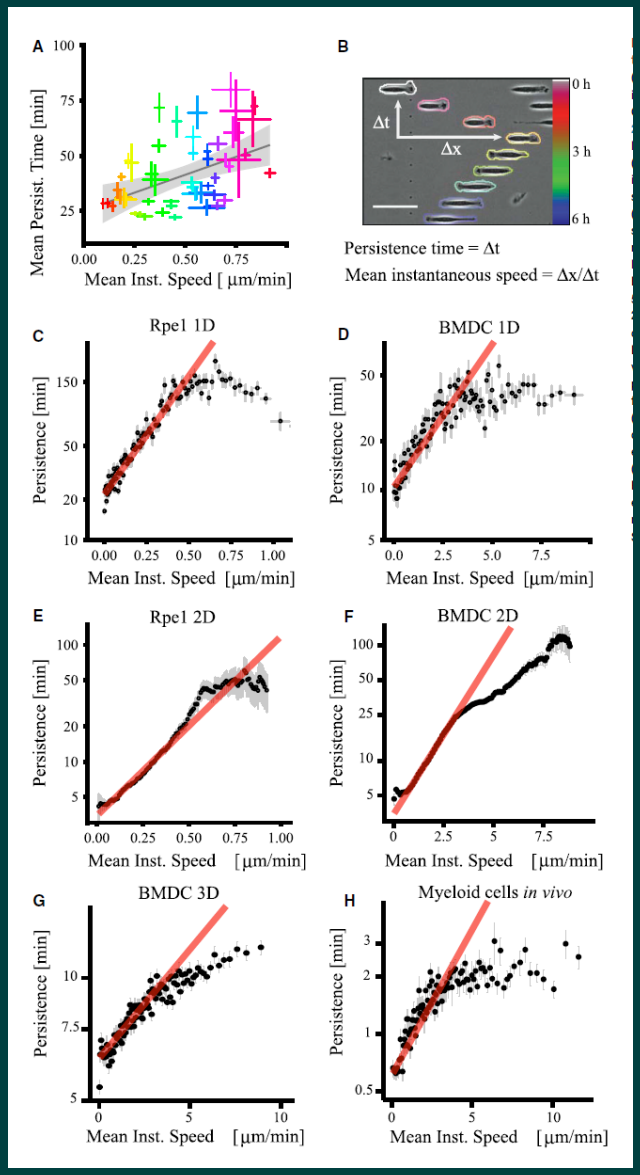


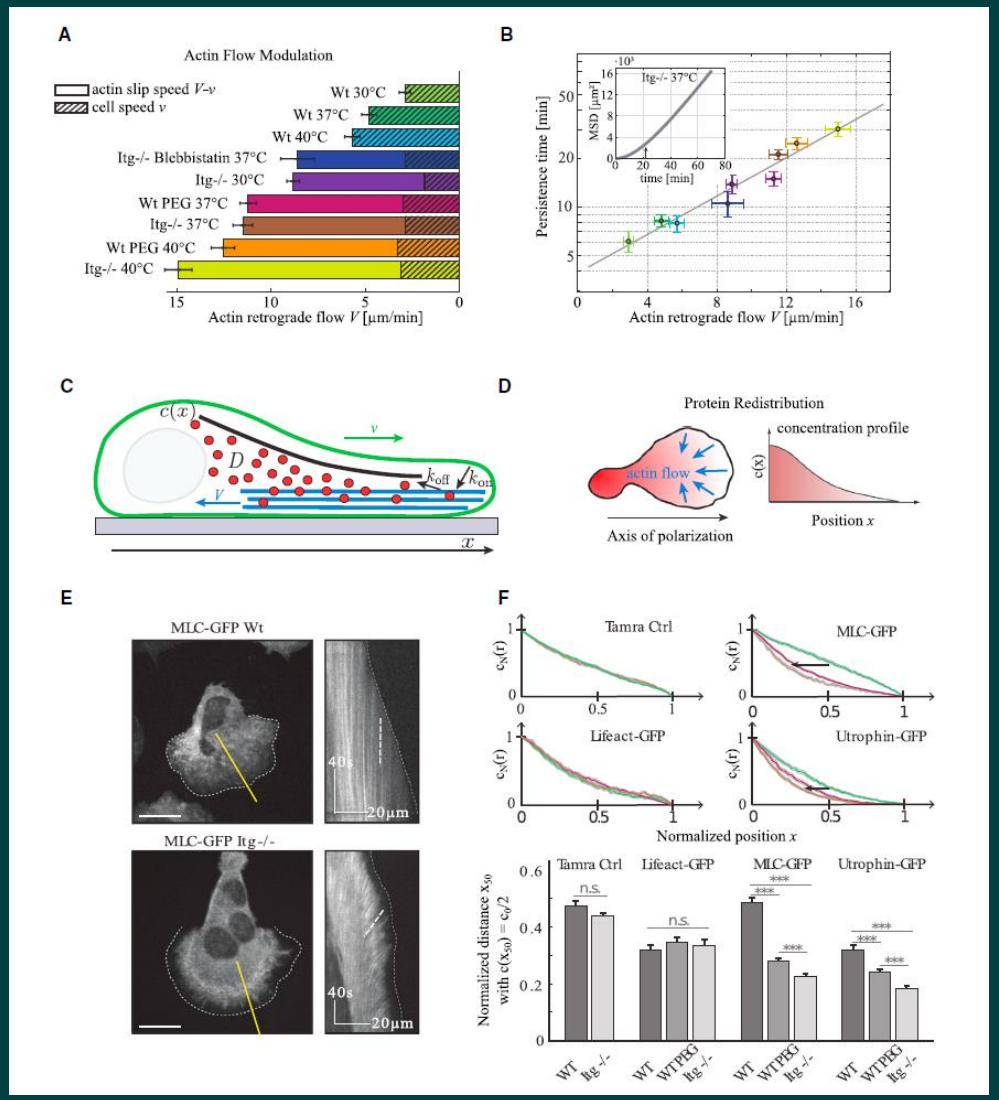


Verkhovsky et al., Curr. Biol., 1999

recent study investigates the relationship between polarity and motion: Maiuri et al., 2015

Actin flow mediate a universal coupling between cell speed and persistence





Maiuri et al., 2015

Diffusible molecules can develop polarized patterns

THE CHEMICAL BASIS OF MORPHOGENESIS

By A. M. TURING, F.R.S. *University of Manchester*

(*Received* 9 *November* 1951—*Revised* 15 *March* 1952)

It is suggested that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis. Such a system, although it may originally be quite homogeneous, may later develop a pattern or structure due to an instability of the homogeneous equilibrium, which is triggered off by random disturbances. Such reaction-diffusion systems are considered in some detail in the case of an isolated ring of cells, a mathematically convenient, though biologically unusual system.

be given. In the continuous form of the theory the concentrations and diffusibilities of each substance have to be given at each point. In determining the changes of state one should take into account

(i) The changes of position and velocity as given by Newton's laws of motion.

(ii) The stresses as given by the elasticities and motions, also taking into account the osmotic pressures as given from the chemical data.

(iii) The chemical reactions.

(iv) The diffusion of the chemical substances. The region in which this diffusion is possible is given from the mechanical data.

example: two cells, two morphogens

$dX/dt = 5X - 6Y + 1$

$dY/dt = 6X - 7Y + 1$

diffusion rates 0.5 for X and 4.5 for Y

Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, Vol.
237, No. 641. (Aug. 14, 1952), pp. 37-72.
Stable URL:
http://links.jstor.org/sici?sici=0080-4622%2819520814%29237%3A641%3C37%3ATCBOM%3E2.0.CO%3B2-I

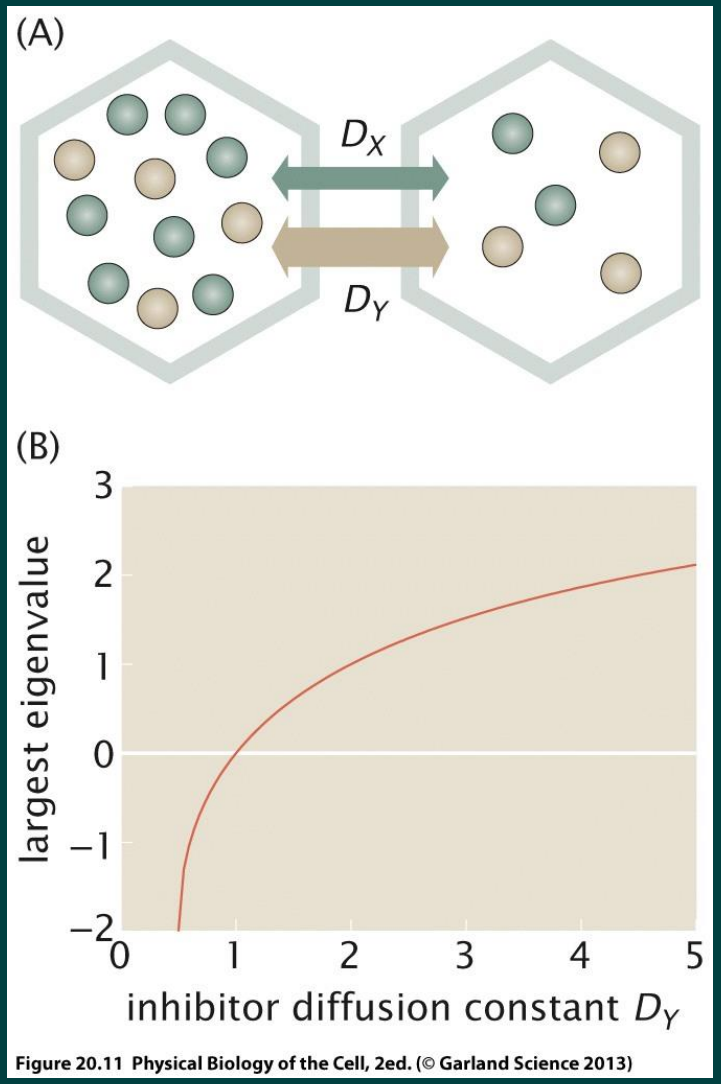


Figure 20.11 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

$$\frac{dX_1}{dt} = 5X_1 - 6Y_1 + 1 + D_X(X_2 - X_1)$$
$$\frac{dY_1}{dt} = 6X_1 - 7Y_1 + 1 + D_Y(Y_2 - Y_1),$$
$$\frac{dX_2}{dt} = 5X_2 - 6Y_2 + 1 + D_X(X_1 - X_2)$$
$$\frac{dY_2}{dt} = 6X_2 - 7Y_2 + 1 + D_Y(Y_1 - Y_2),$$

in two cells, instability develops if diffusion of the inhibitor (Y) is faster than that of the activator (X)

Patterns in the skin of different cats are reproduced well with reaction-diffusion mechanism despite the fact that the physical mechanism in the skin is likely not diffusion

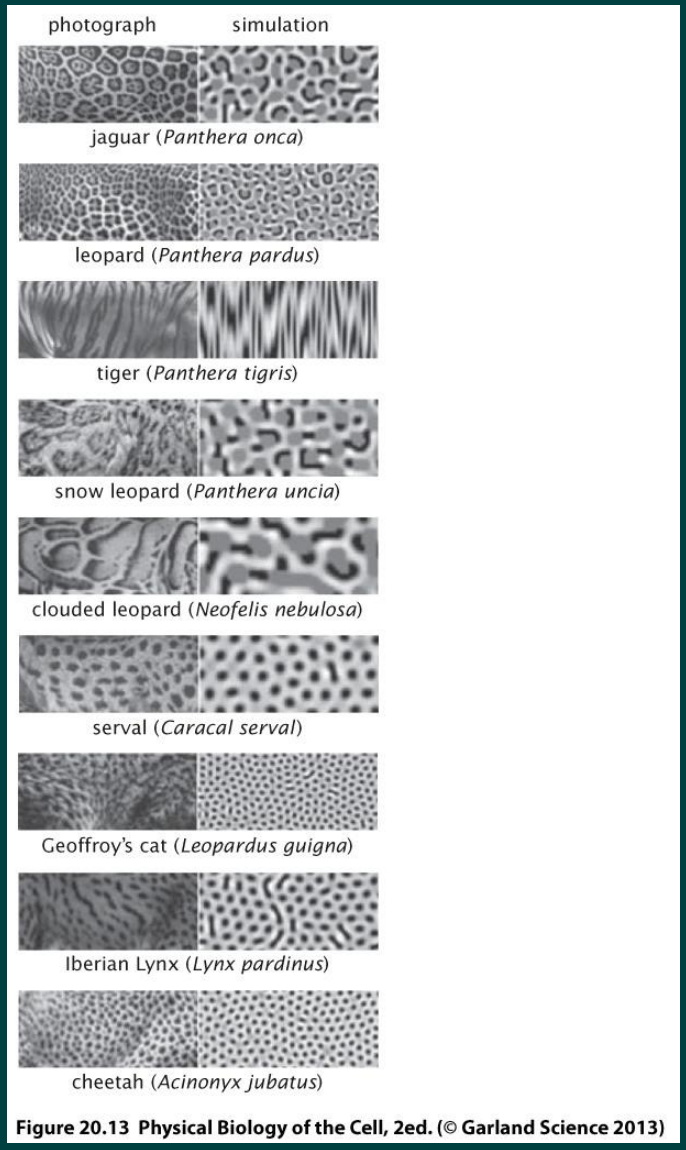


Figure 20.13 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Are there reaction-diffusion mechanism in the cells?

What are X and Y?

Examples:

bacterial Min proteins (C, D and E)

eukaryotic small GTPases of Rho-family