Lecture 1: cells and tissues as active contractile matter

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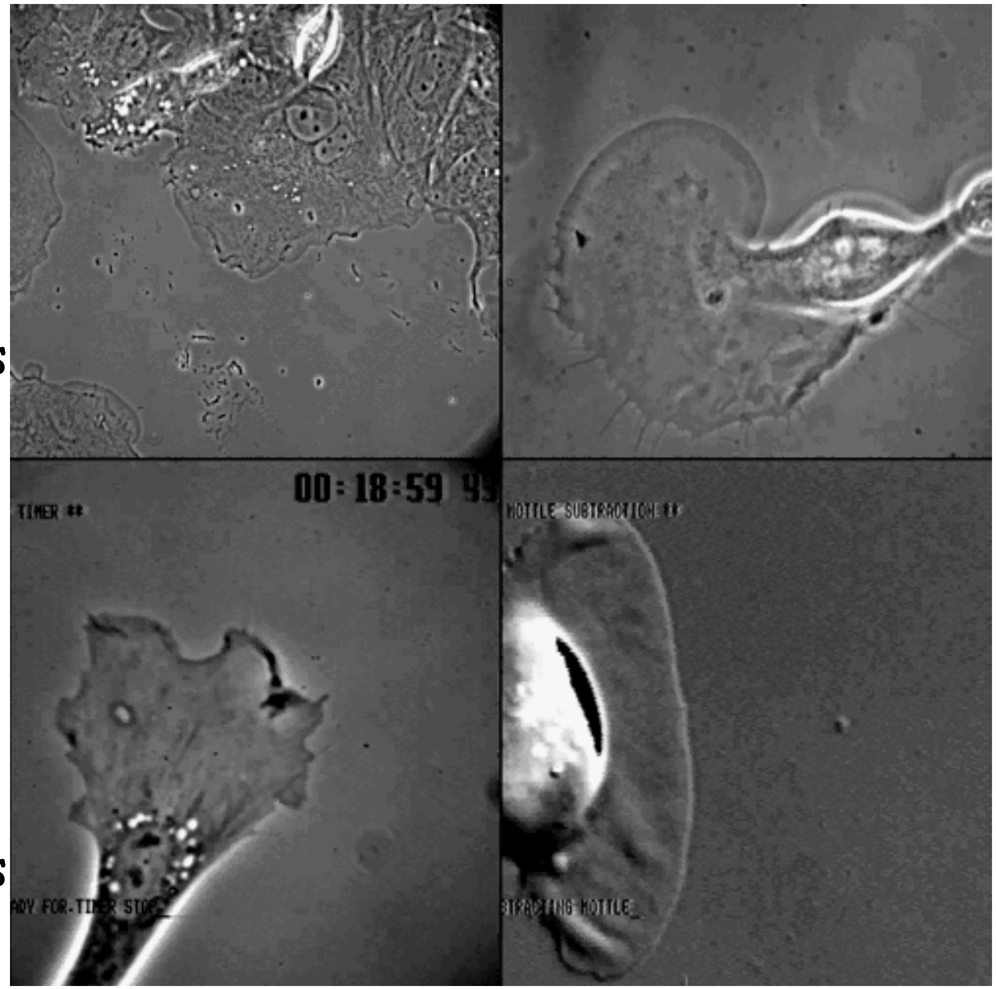
Crawling Cells as Active Matter

mouse fibroblasts (3h)

mouse melanoma (20min)



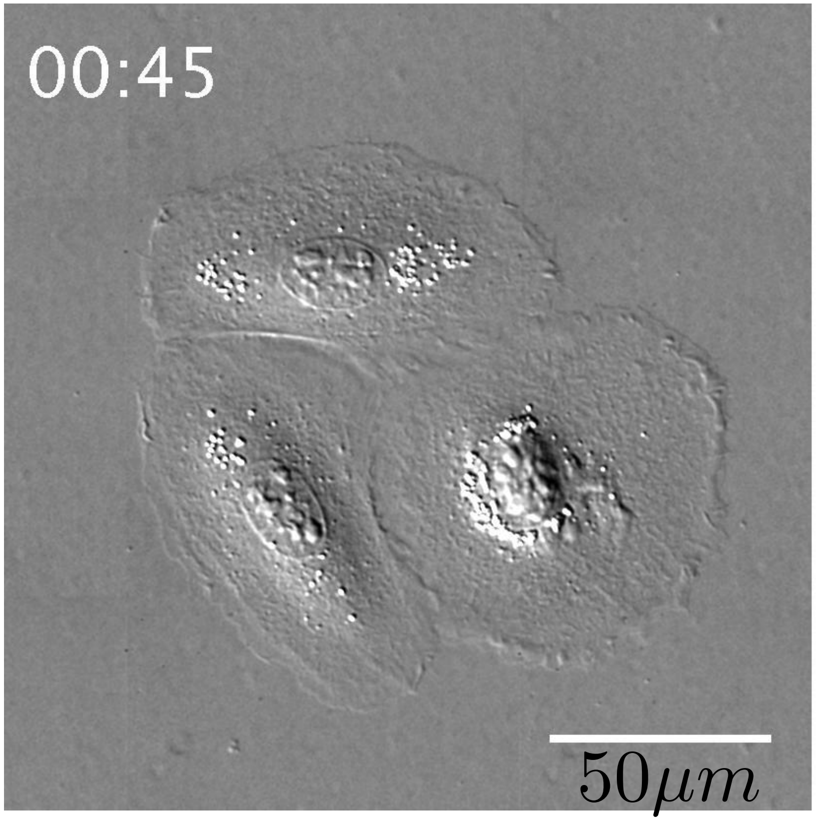
chick fibroblasts (2h)

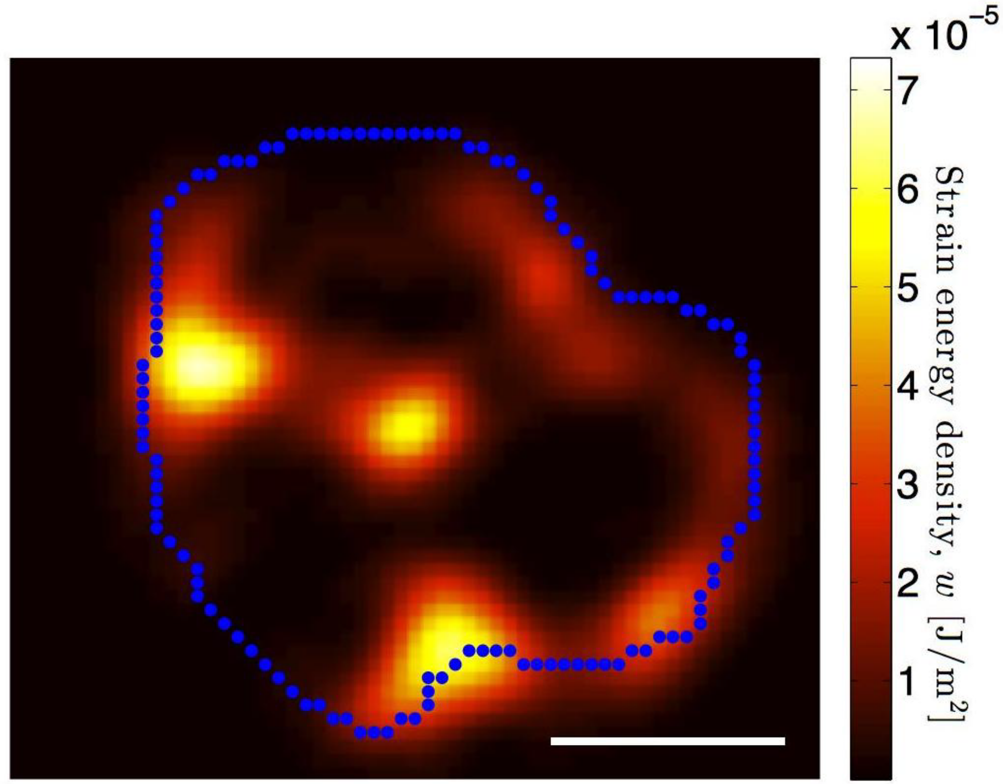
trout keratocyte (4min) v=15μm/min

V. Small, IMBA, Vienna.

Adherent Cells as Active Matter

Cells actively generate forces & transmit them to the environment





Mouse keratinocytes, A.F. Mertz et al., **PNAS 2013**

Outline

- Introduction: mechanical properties & topology of the environment affect cell behavior: shape, spreading, motility, interactions, …
- Continuum model of cells as active, contractile elastic media (≠ active liquids → Sriram Ramaswamy)
- Polarized cells
- From cells to tissues: emergence of mechanical properties of tissues from cell-cell and cell-substrate interactions
- Collective cell migration

Some references

Review:

- U. Schwarz & S. Safran, RMP **85**, 1327 (2013).

Our work:

- S. Banerjee & MCM, EPL **96**, 28003 (2011); PRL **109**, 108101 (2012).
- A. Mertz et al, PRL **108**, 198101 (2012); PNAS **110**, 842 (2013).
- P. Oakes et al, Biophys. J. (2014) to appear.
- S. Banerjee, R. Sknepnek & MCM, Soft Matter **10**, 2424 (2014).

Theory

Shiladitya Banerjee
Syracuse → Chicago

Rastko Sknepnek
Syracuse
→ Dundee,UK

Kazage Utuje
Syracuse

Experiments

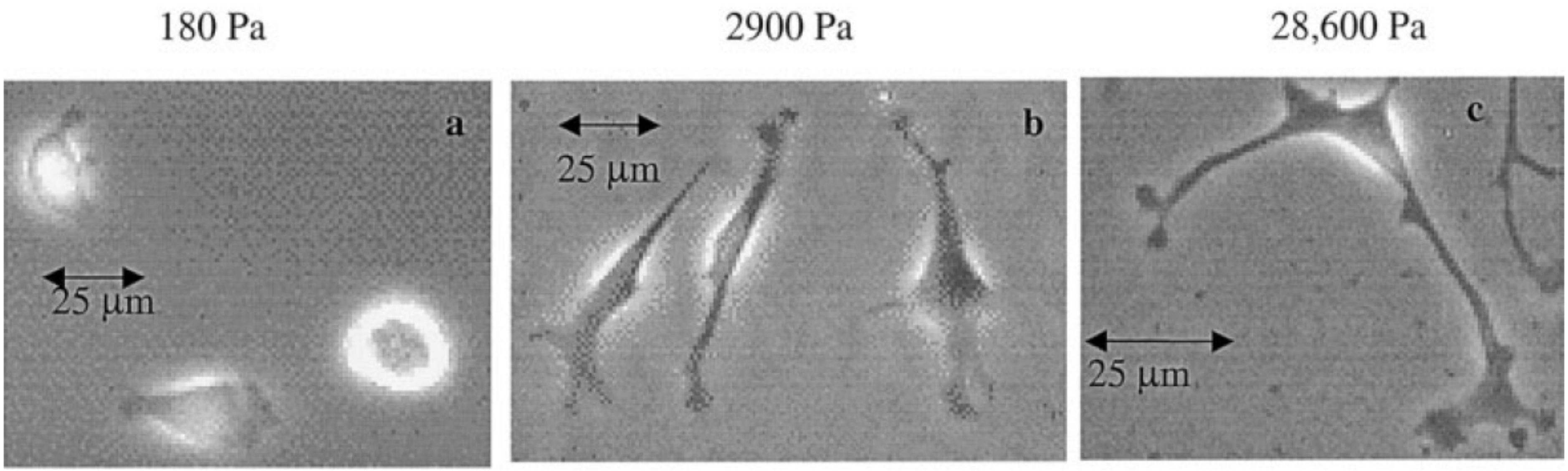
Eric Dufresne
Yale

Aaron Mertz
Yale
→ Rockefeller

Margaret
Gardel
Chicago

Patrick Oakes
Chicago

Substrate stiffness affects cell shape

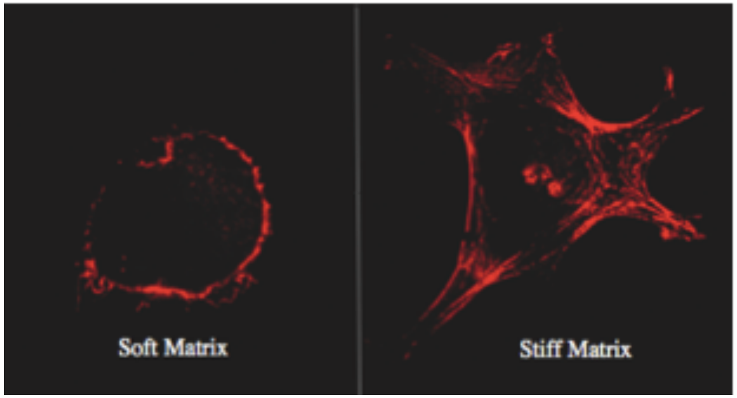


Soft substrates: small, round cells

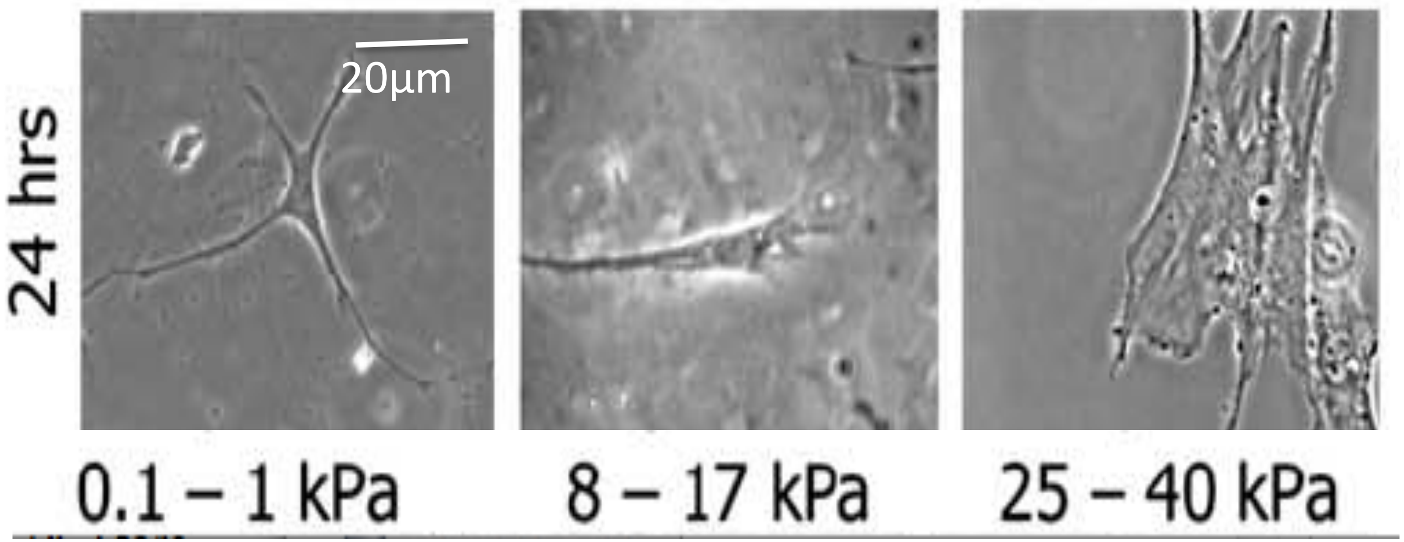
Hard substrates: spread, branched cell shapes

Janmey's Lab (Upenn) : endothelial cells on polyacrylamide gels
(Yeung et al, Cell Mot. & Cytoskeleton, 2006)

Cell spreading accompanied by the appearance of stress fibers → cell polarization.
Pelham & Young PNAS 1997



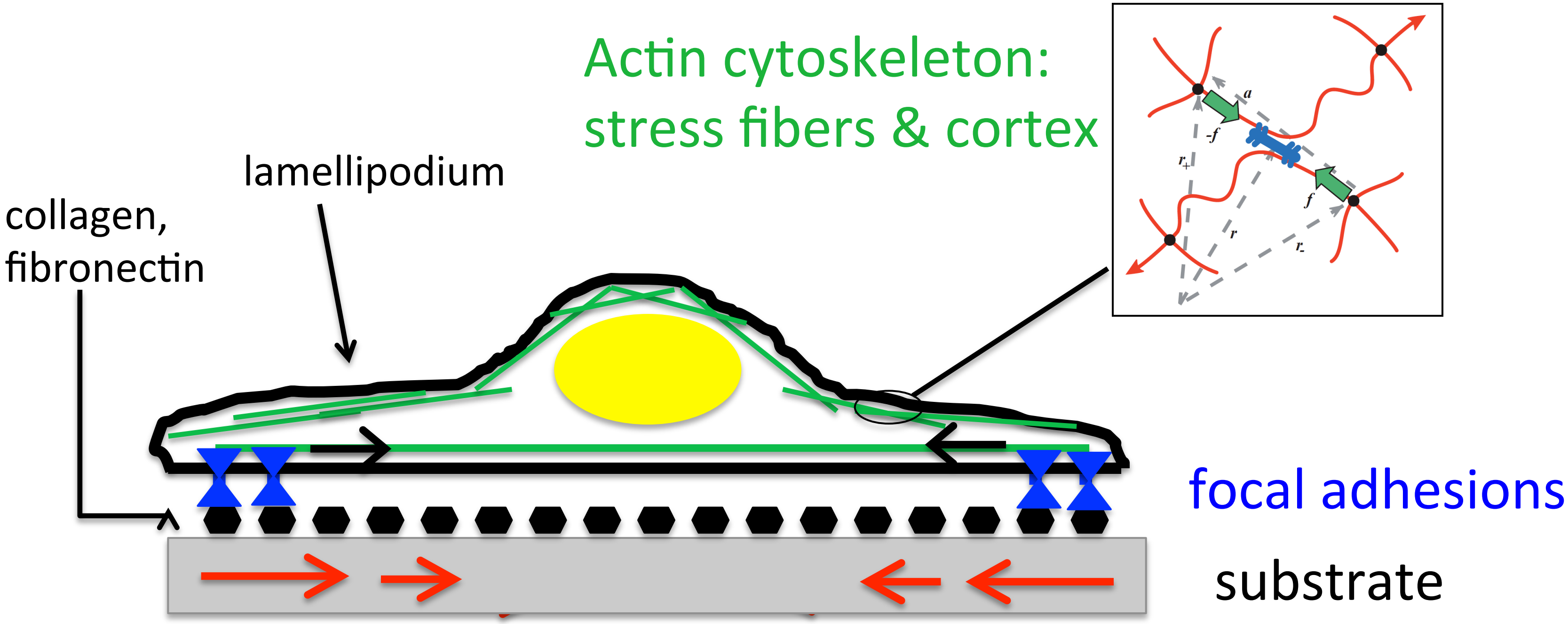
Substrate stiffness may affect cell differentiation



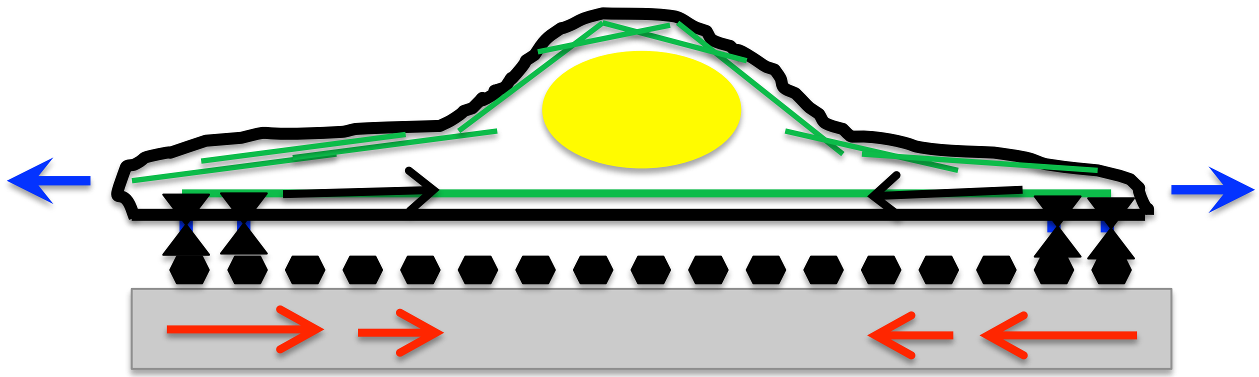
Discher Lab (Upenn): mesenchymal stem cells
(Engler et al, Cell 2006)

Cell adhesion: relevant cellular machinery

- Contractile forces are generated by myosins in the actin network
- Actin polymerization in the lamellipodium
- Forces are transmitted to the extracellular matrix (ECM) via focal adhesions → **traction stresses in the substrate**



Forces in adherent cells



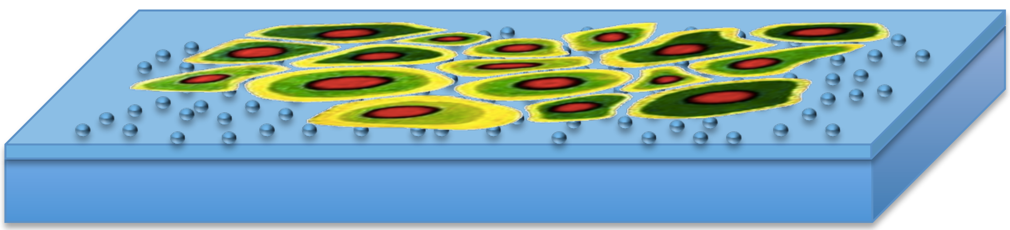
- Inward pull by myosin contraction
- Outward push on lamellipodium by actin polymerization

In a stationary cell net traction pattern on substrate is a **contractile force dipole**

Measuring Traction Stresses

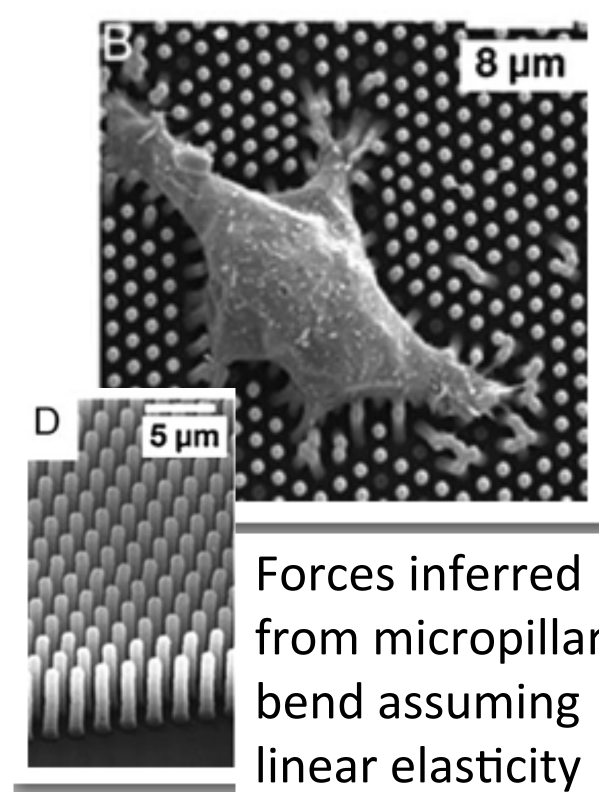
Traction Force Microscopy (TFM)

Polystyrene beads, r~100 nm



Traction stresses inferred with linear elasticity from displacements of embedded beads
(Dembo & Wang, 1999)

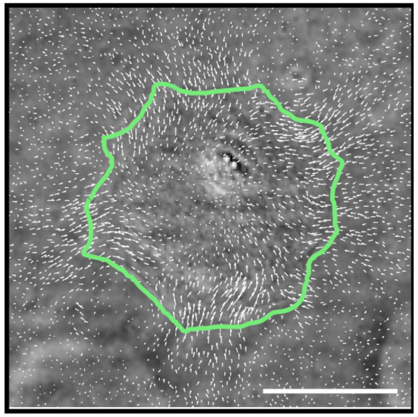
Microfabricated Pillar Arrays



Forces inferred from micropillars bend assuming linear elasticity
(Tan et al, 2003)

Inferring traction stresses from FTM

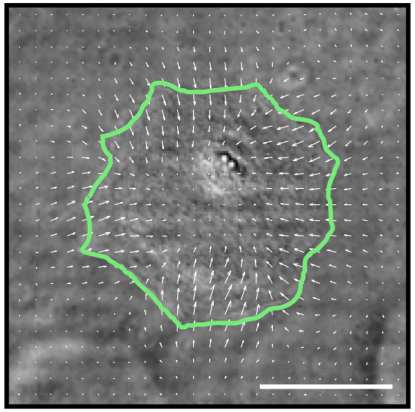
Measure substrate deformation



Substrate displacement field

$$\mathbf{u}_s$$

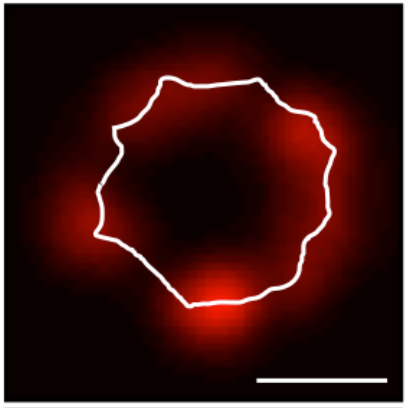
Infer traction stresses



Traction stress

$$\mathbf{T} = \mathbf{G}_{elastic}^{-1} * \mathbf{u}_s$$

Energy spent by cell to deform the substrate



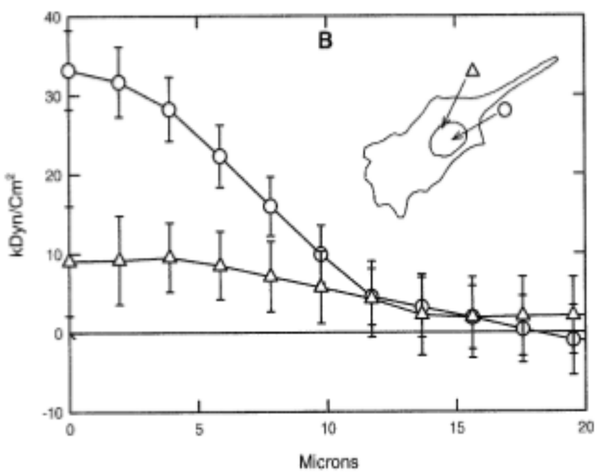
Strain energy

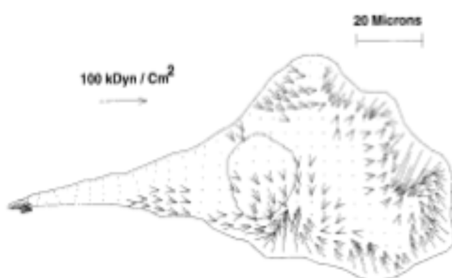
$$W = \frac{1}{2} \int dA \; \mathbf{T}(\mathbf{r}) \cdot \mathbf{u}_s(\mathbf{r})$$

Stationary keratinocytes

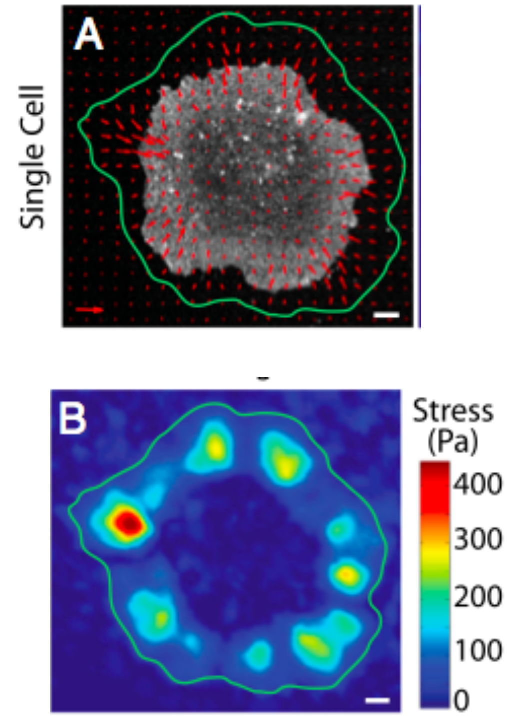
Mertz, Banerjee et al, PRL, 2012

Traction stresses are localized at the cell edge





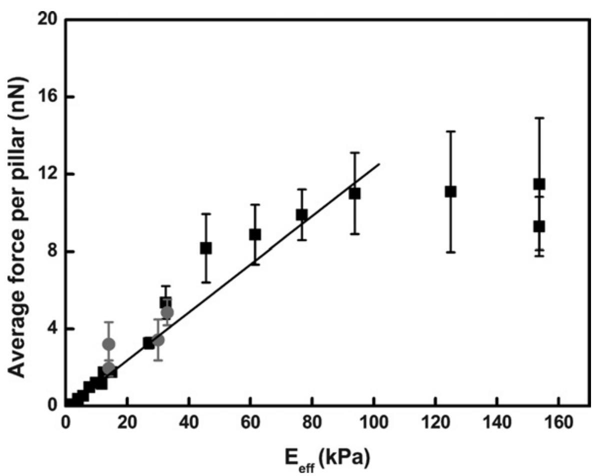
Fibroblast: Dembo & Wang Biophys J 76, 2307 (1999).



MDCLK cell: Maruthamuthu et al PNAS 2011

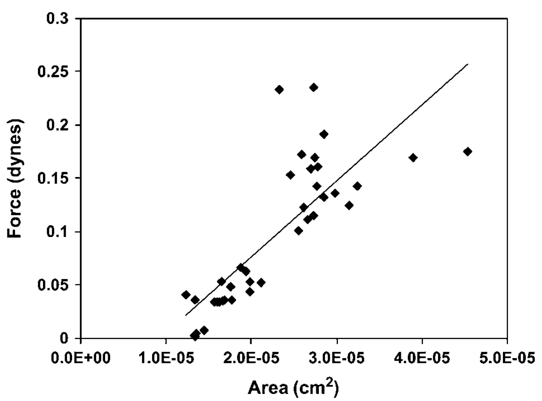
What controls and regulates force generation by adherent cells?

Force increases and saturates with substrate stiffness



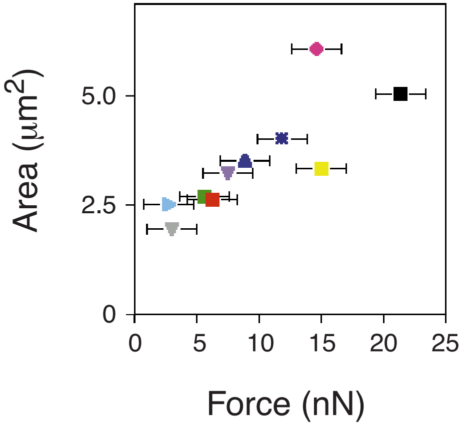
M. Ghibaudo *et al,* Soft Matter 2008.

Force increases with cell area



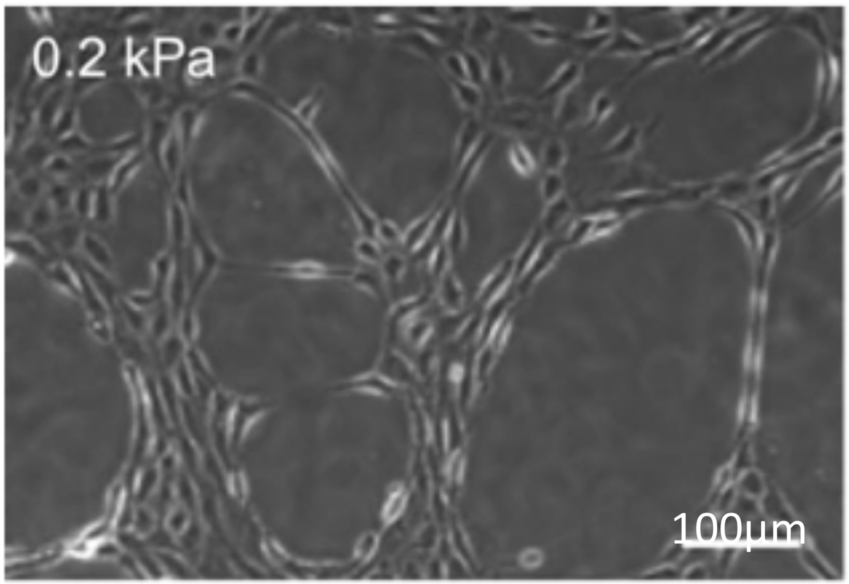
Reinhart-King *et al,* Biophys J. 2005.

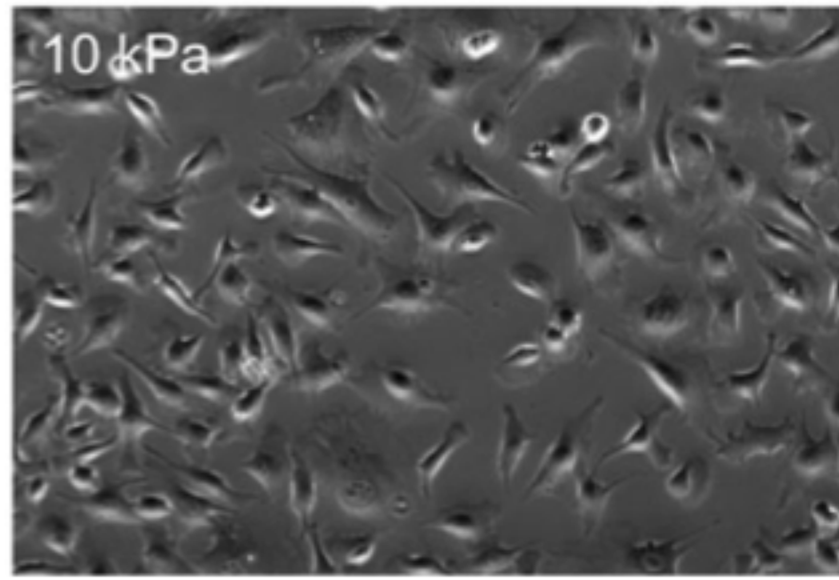
Force increases with area of focal adhesions



Balaban et al, Nat. Cell. Bio. 2001

Substrate stiffness affects cell organization and cell network assembly





Reinhart-King Lab (Cornell): endothelial cells on polyacrylamide

Califano et al, Cell.Mol. Bioeng. 1:122 (2008)

Mechanical interaction of cells with environment affects many cell functions:

- motion
- shape
- growth
- differentiation

Individual cells:

- Which cellular components control force generation and regulation?
- Which properties of ECM affect force generation?

Collective cell behavior:

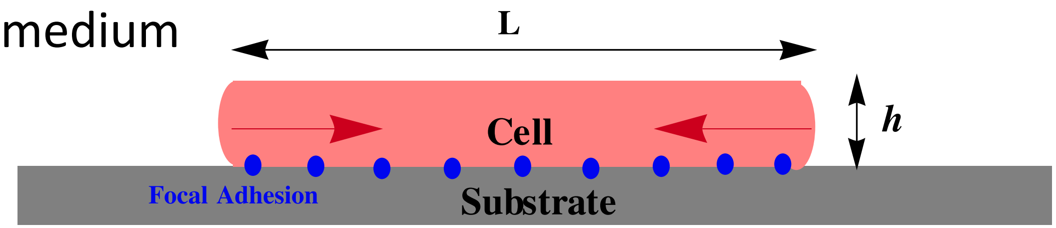
- How do the mechanical interactions among cells and of cells with the environment affect cell organization?
- How do the mechanical properties of tissues emerge from the interplay of cell-cell and cell-medium interactions?

Modeling adherent cells as contractile active elastic media

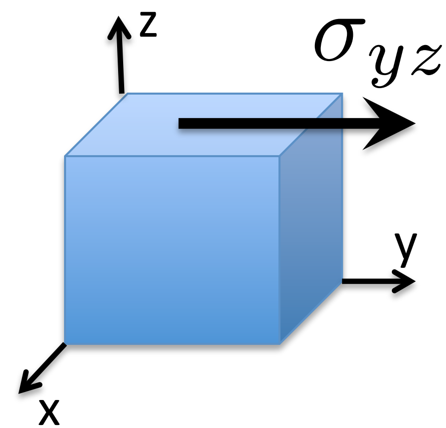
Contractile ``cell" on stiff substrate

S. Banerjee & MCM EPL 2011; Edwards & Schwarz, PRL 2011

- cell as an elastic isotropic active medium
- h<<L
- thin substrate
- only in plane stresses



$\sigma_{\alpha\beta}$ stress tensor of cellular material: α-th component of force on a unit area normal to β direction



Force balance: $\partial_\beta \sigma_{\alpha\beta} = 0 \ (\alpha, \beta \in x, y, z)$

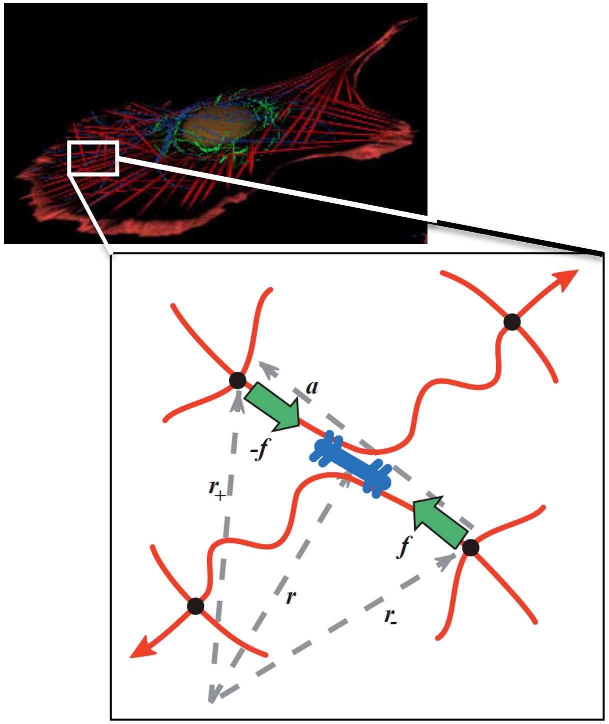
$$\sigma_{\alpha\beta} = \sigma^{el}_{\alpha\beta} + \sigma^{a}_{\alpha\beta}$$

active stress

$$\sigma^{el}_{\alpha\beta} = B u_{\gamma\gamma}\delta_{\alpha\beta} + 2\mu \left(u_{\alpha\beta} - \frac{1}{3}\delta_{\alpha\beta} \right)$$

B compressional modulus

μ shear modulus



Active stress

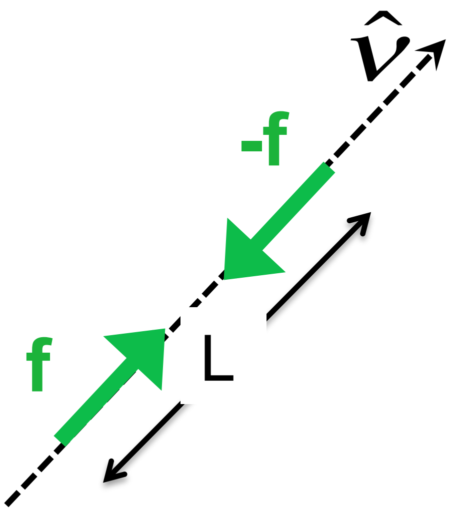
Myosin clusters exert contractile force dipoles on the surrounding medium resulting in active stresses

Force balance: $\partial_\beta \sigma^{el}_{\alpha\beta} = -F^{active}_\alpha$

$$\vec{F}^{active} = \left\langle \sum_{\substack{\text{active} \\ \text{units n}}} \left[-f\hat{v}_n \delta(\vec{r} - \vec{R}_n - \frac{L}{2}\hat{v}_n) + f\hat{v}_n \delta(\vec{r} - \vec{R}_n + \frac{L}{2}\hat{v}_n) \right] \right\rangle$$

$$\simeq \vec{\nabla} \cdot \left[fL \left\langle \sum_n \hat{v}_n \hat{v}_n \delta(\vec{r} - \vec{R}_n) \right\rangle + \ldots \right]$$

$$\simeq fL \vec{\nabla} \cdot \left[\tfrac{1}{d} \rho_m \mathbf{1} + \mathbf{pp} \right] \equiv \vec{\nabla} \cdot \vec{\sigma}^{active}$$



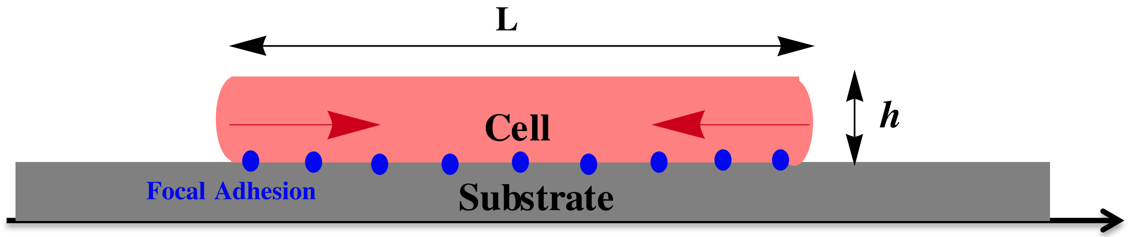
$$\sigma^{active}_{\alpha\beta} = \sigma_a \delta_{\alpha\beta} + \alpha P_\alpha P_\beta$$

contractile "pressure" $\sigma_a > 0$

active stress coupled to cell polarization

Effective 2D model

Average over cell thickness h



$$\int_0^h dz\,[\partial_j \sigma_{ij} + \partial_z \sigma_{iz}] = 0 \qquad i,j = x,y$$

$$h\partial_j \overline{\sigma}_{ij} + \sigma_{iz}(h) - \sigma_{ij}(0) = 0 \qquad \overline{\sigma}_{ij}(\mathbf{r}) = \int_0^h \frac{dz}{h}\sigma_{ij}(\mathbf{r},z)$$

$$\sigma_{iz}(h) = 0$$

$$\sigma_{iz}(0) = T_i$$

Traction by cell on substrate

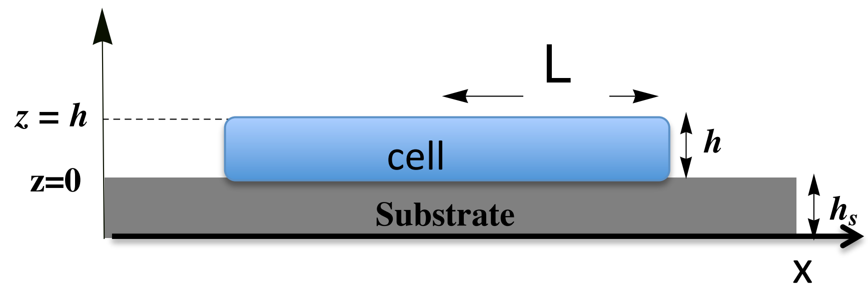
$$h\partial_j \overline{\sigma}_{ij} = T_i$$

$$[\sigma_{ij} n_j]_{\partial cell} = 0$$

One-dimensional ``cell" on stiff substrate

S. Banerjee & MCM EPL 2011; Edwards & Schwarz, PRL 2011

- cell as an elastic isotropic active medium
- h<<L, thin substrate



Force balance → $\partial_x \sigma_{xx} + \partial_z \sigma_{xz} = 0$

$$\sigma(x) = \frac{1}{h}\int_0^h dz \sigma_{xx}(x,z), \qquad \sigma = B\partial_x u + \sigma_a$$

$$h\partial_x \sigma + \sigma_{xz}(h) - \sigma_{xz}(0) = 0$$

$$\sigma_{xz}(x, z = L) = 0$$

$$\sigma_{xz}(x, z = 0) = Y u_x(x, z = 0) = T(x)$$

$$\sigma = \ell_p^2 \frac{d^2\sigma}{dx^2} + \sigma_a$$

$$\ell_p = \sqrt{hB/Y}$$

penetration length: controls spatial variations of substrate-induced deformations

substrate ``rigidity"

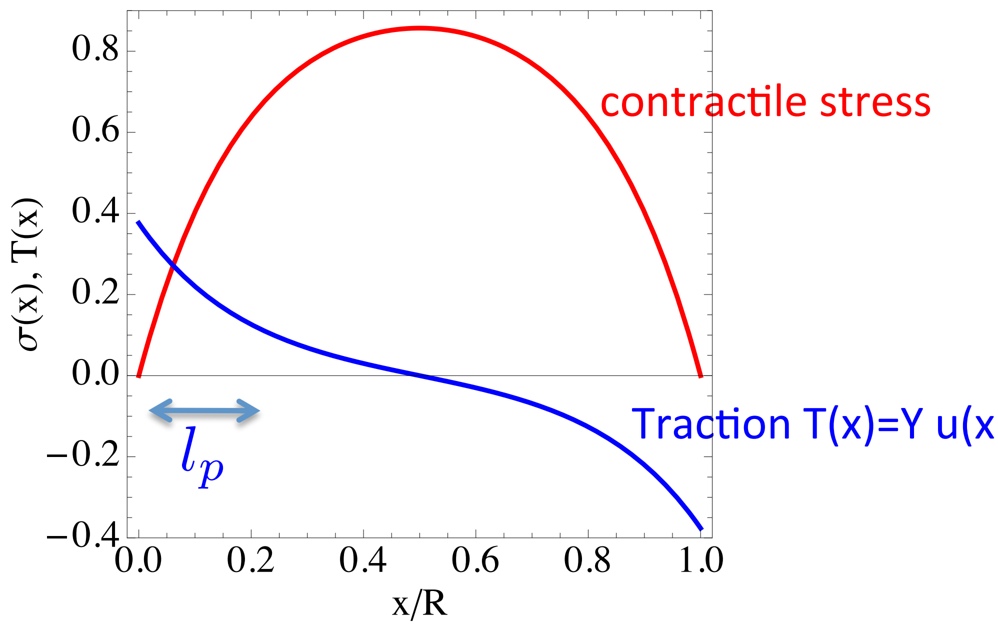
controlled by substrate stiffness & thickness, density and nature of adhesion complexes, …

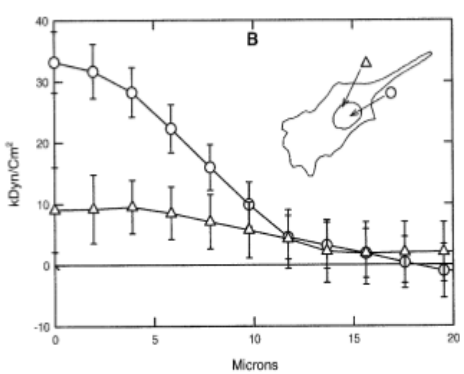
$$\frac{1}{Y} = \frac{1}{\rho_a k_a} + \frac{1}{\mu_s / h_s}$$

$$\sigma = \ell_p^2 \frac{d^2\sigma}{dx^2} + \sigma_a$$

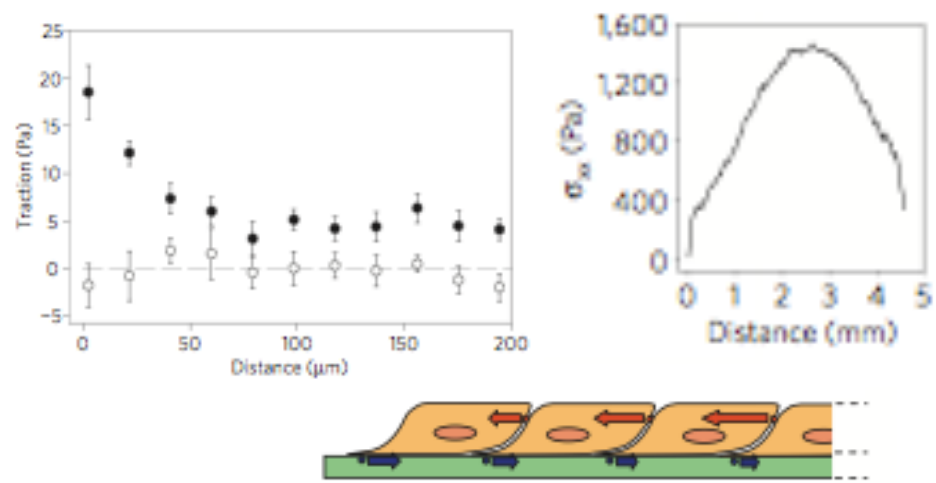
$$\ell_p = \sqrt{\frac{Bh}{Y}}$$

Penetration length:
spatial variation of
traction and cellular stress



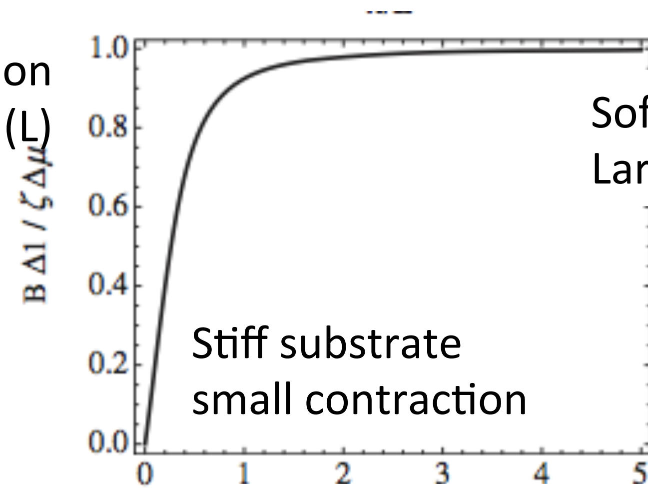


Single fibroblast
Dembo and Wang, Biophys. J. 1999.



Trepat et al, Nat. Phys. 2009. migrating cell colony

Cell contraction largest on soft substrate



Cell contraction
u(0)-u(L)

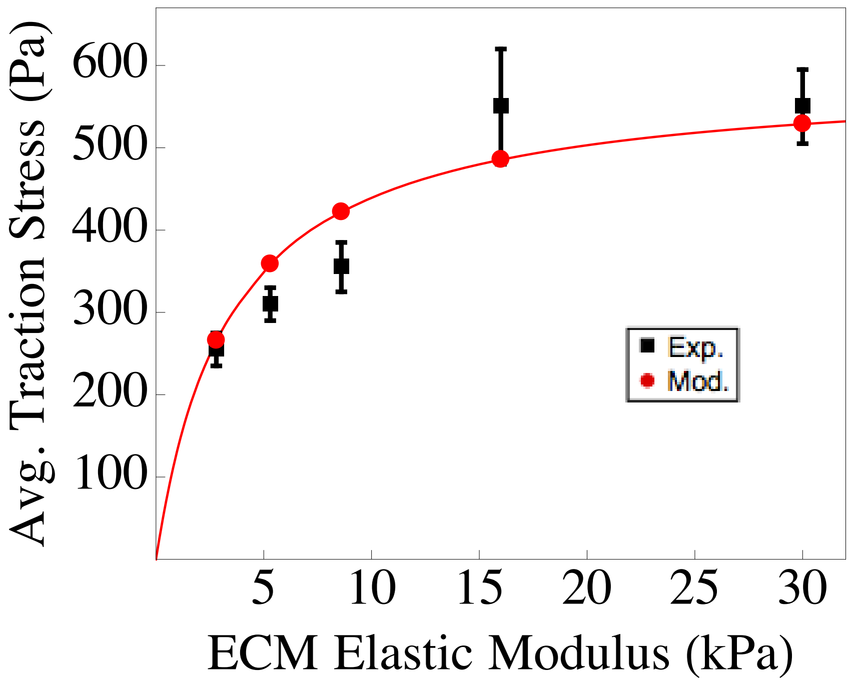
Soft substrate
Large contraction $\sim \sigma_a / B$

Stiff substrate
small contraction

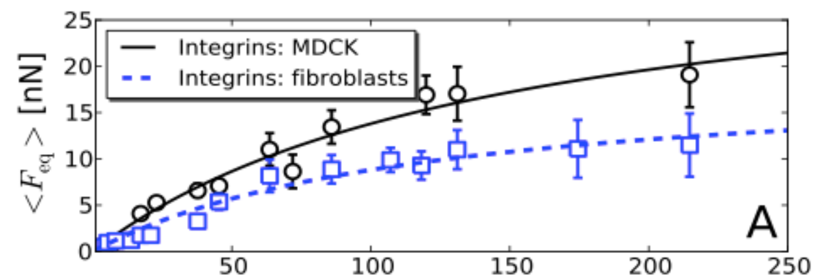
Penetration length $\sim 1/\sqrt{Y}$

Total traction force
increases with substrate stiffness

$$\langle |T| \rangle = \int \frac{d\mathbf{r}}{A} |\mathbf{T}(\mathbf{r})|$$



Oakes et al, Biophys. J. 2014, fibroblasts on patterned substrates



Marcq, Yoshinaga & Prost, Biophys. J. 2011: average traction force/pillar

Some estimates

$$\text{cell modulus } B \sim 10KPa$$

$$\text{cell size } L \sim 10\mu m$$

$$\text{cell thickness } h \sim 1\mu m$$

$$\ell_p \sim 0.1L \to Y = \frac{Bh}{\ell_p^2} \sim 10kPa/\mu m$$

Traction force at saturation $\sim \sigma_a h L$

$$\sigma_a \sim 4 - 10kPa$$

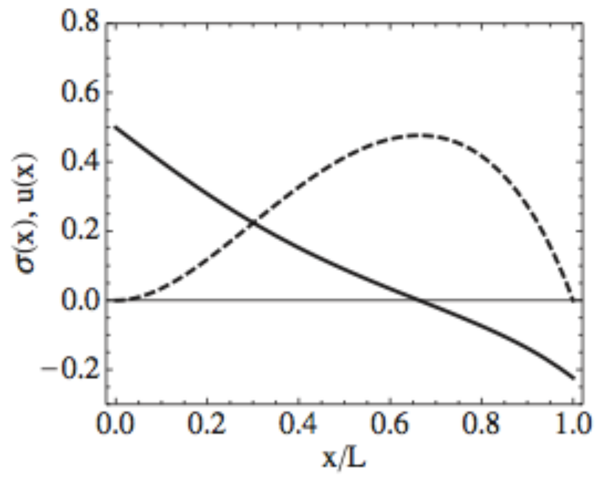
Homework

Find cellular stress and traction profile for a cell on a substrate of varying stiffness:

$$\partial_x \sigma = Y(x) u$$

$$\sigma = B \partial_x u + \sigma_a$$

$$Y(x) = Y_0 x / L$$



Cells are known to migrate towards stiffer regions → durotaxis

Can this model suggest a possible mechanism that drives durotaxis?

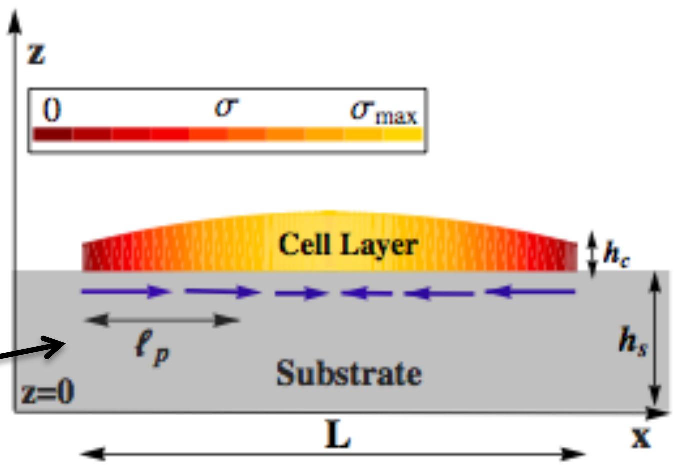
S.Banerjee & MCM, PRL 2012

Effect of substrate thickness on force transmission

$$\ell_a^2 \partial_x^2 \sigma + \sigma_a = \sigma - \ell_s^2 \partial_x^2 \int_0^L dx' G(x-x')\sigma(x')$$

nonlocal substrate elasticity

A cell of lateral extent L ``feels'' a thickness L of the substrate



nonlocal elastic response

$$\ell_p \simeq \sqrt{B_c h_c \left(\frac{1}{Y_a} + \frac{h_{eff}}{E_s} \right)}$$

$$h_{eff} \sim \left(\frac{1}{L} + \frac{1}{h_s} \right)^{-1}$$

$$h_{eff} \sim h_s \quad L \gg h_s$$

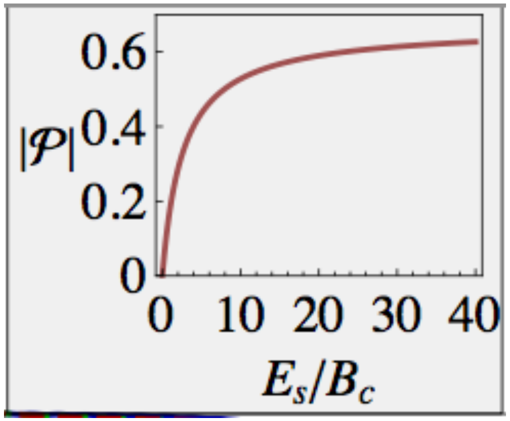
$$h_{eff} \sim L \quad L \ll h_s$$

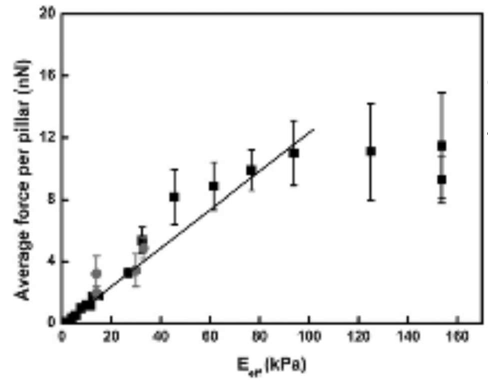
$$E_s \sim 0.01 - 100 kPa \;\rightarrow\; \ell_p \sim 0.35 - 35 \mu m$$

$$(h_s \gg L \sim 100 \mu m)$$

Effect of substrate stiffness E_s and thickness h_s

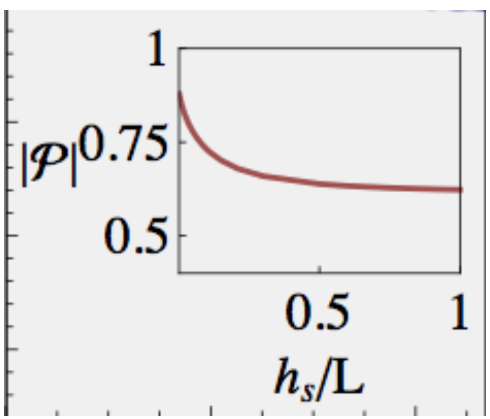
- Traction increases with stiffness and saturates

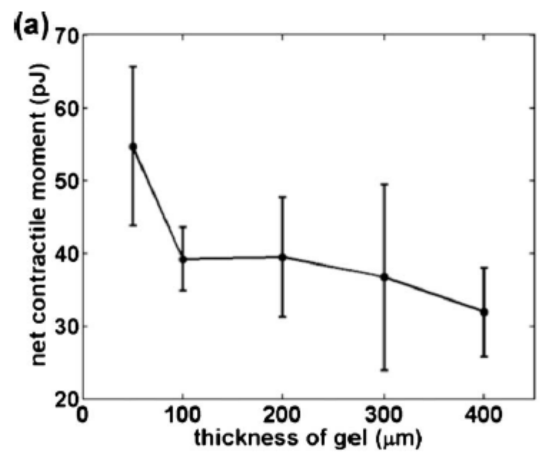




Ghibaudo et al.
Soft Matter, 2008
MDCK cells

- Traction decreases with increasing thickness

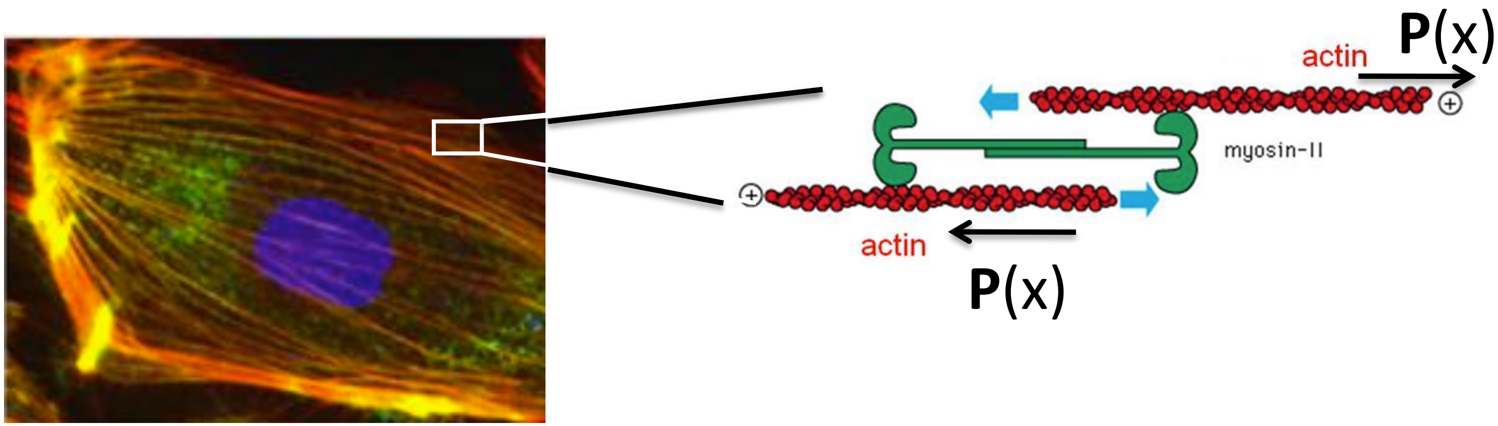




Lin et al. PRE 2010
fibroblasts

Cell Polarization

A variety of ATP-driven processes (treadmilling, myosin-driven contractility) can yield the build-up of cell polarization (e.g., stress fibers)



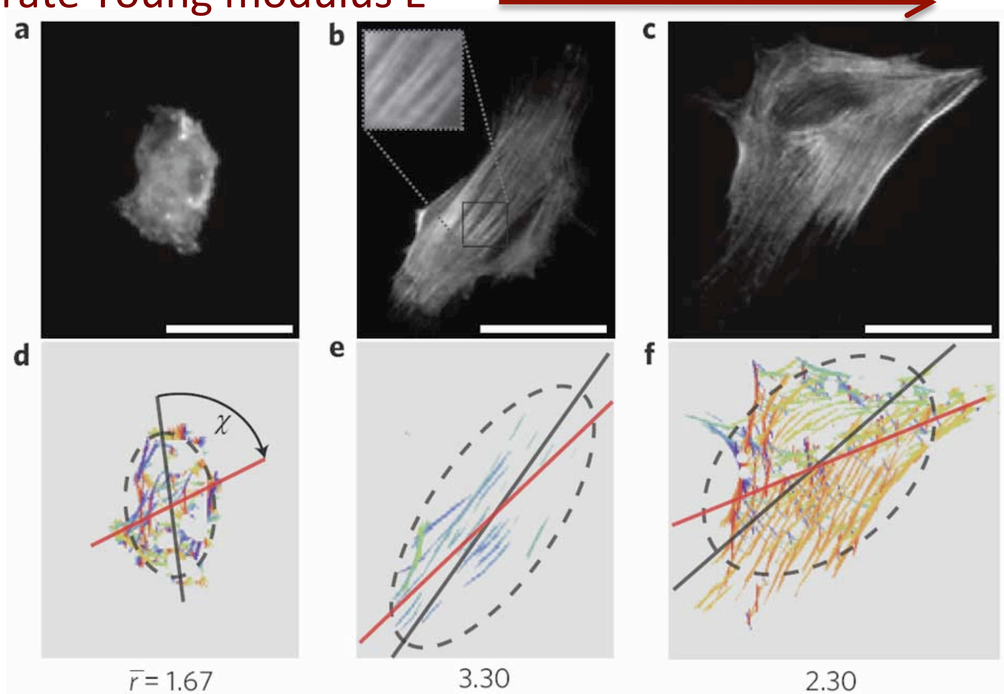
Cell polarization is described by a vector field **P**(x) that couples to active stresses and passive elastic stresses in the cytoskeleton.

Optimal matrix rigidity for stress-fibre polarization in stem cells

A. Zemel, F. Rehfeldt, A. E. X. Brown, D. E. Discher & S. A. Safran

Nature Physics **6**, 468–473 (2010)

Substrate Young modulus E →



E=1kPa E=11kPa E=34kPa

Model of cell as a polarizable inclusion in a passive elastic medium supports experiments

Continuum model of polarized cell

displacement $\mathbf{u}(\mathbf{r})$

polarization $\mathbf{P}(\mathbf{r})$

$$u_{ij} = \frac{1}{2}\left(\partial_i u_j + \partial_j u_i\right)$$

$$F = \int_{\mathbf{x}} \frac{B}{2}(\nabla.\mathbf{u})^2 + \mu u_{ij}u_{ij} + \frac{a}{2}\mathbf{P}^2 + \frac{b}{4}\mathbf{P}^4 + \frac{K}{2}(\partial_i P_j)^2 + w\partial_i P_j u_{ij} + \sigma^a_{ij} u_{ij}$$

$$h\partial_j \sigma_{ij} = Y u_i$$

$$\partial_t \mathbf{P} + \beta(\mathbf{P}\cdot\nabla)\mathbf{P} = \Gamma \mathbf{h}$$

$$\sigma_{ij} = \frac{\delta F}{\delta u_{ij}}$$

$$\mathbf{h} = -\frac{\delta F}{\delta \mathbf{P}}$$

Active stress $\sigma^a_{ij} = \sigma_a \delta_{ij} + \alpha P_i P_j$

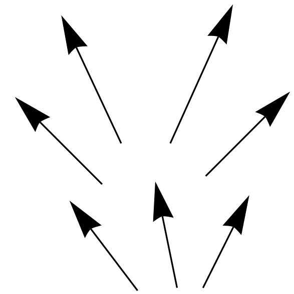
SB and MCM, EPL (2011).

Polarization – Strain Coupling : $w(\partial_i P_j)u_{ij}$

$w > 0$

$\nabla.\mathbf{u} < 0$ (Contractile)

=>

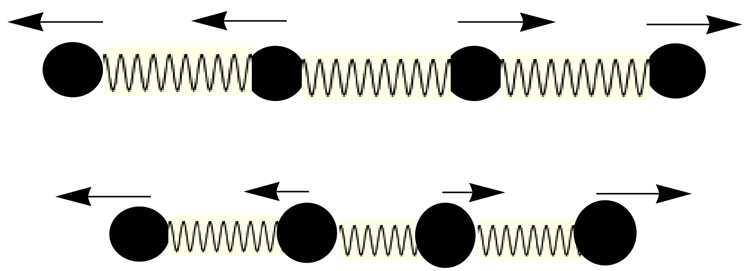


$\nabla.\mathbf{P} > 0$

Positive Splay

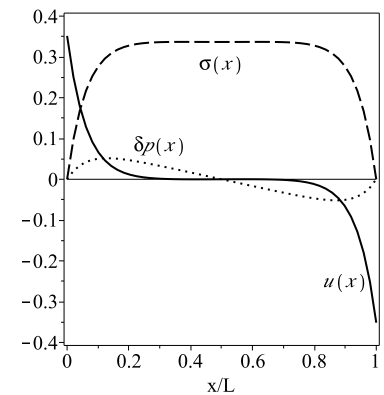
Effective 1D Picture

$b > 0$

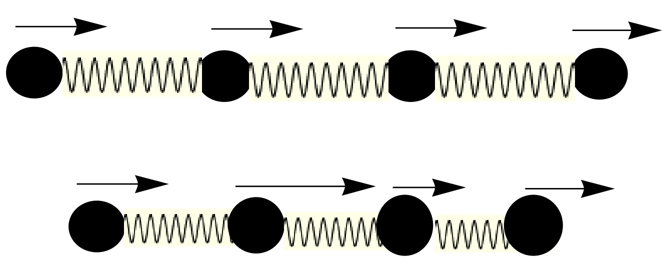


Isotropic

$\langle \delta p \rangle = 0$

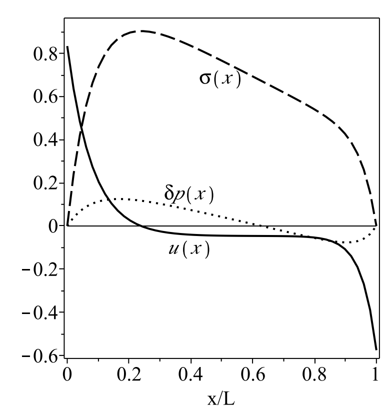


$b < 0$



Polarized

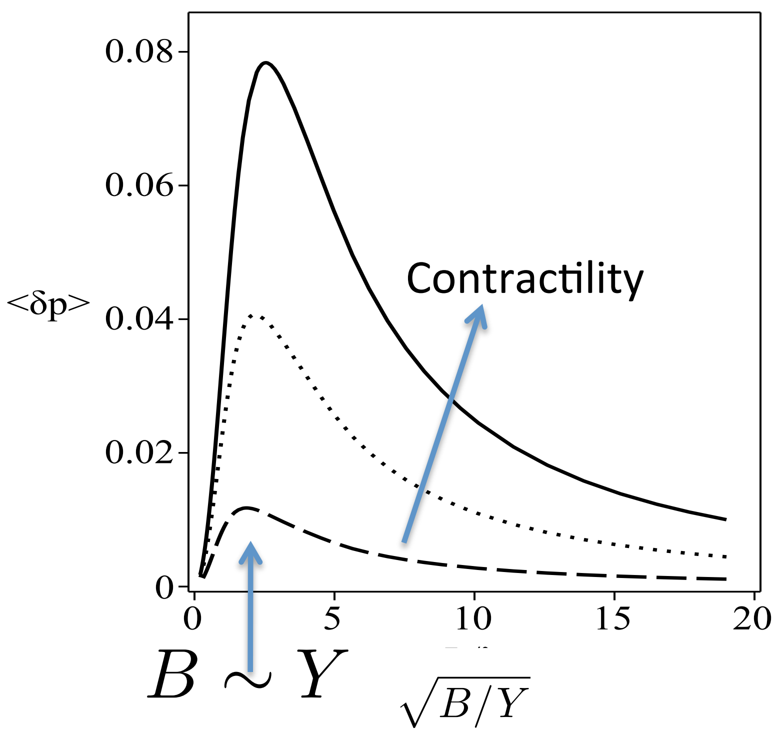
$\langle \delta p \rangle \neq 0$



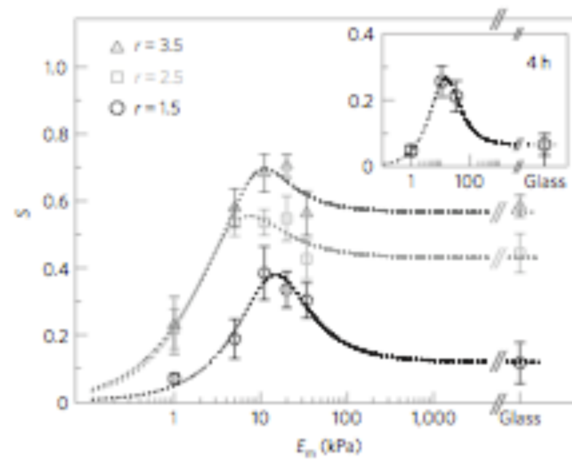
Thin Film of Polarized Cell

P_0 polarization before adhesion

$\delta \bar{P} = \int_0^L \frac{dx}{L}\left[P(x) - P_0\right]$ excess polarization after adhesion



δP non-monotonic function of substrate compliance.

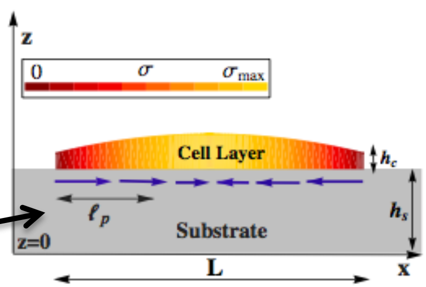


A. Zemel et al, Nat. Phys. 2010

Maximal polarization is induced when elastic modulus of the cell layer is comparable to that of the compliant environment -$B \sim Y$

Interim Summary

- ❑ Cell modeled as continuum contractile elastic medium
- ❑ Minimal model yields several experimentally relevant results:
  - Built-up of contractile stresses at cell center
  - Localization of traction stresses at cell edges
  - Total traction stress increases with substrate stiffness
  - Optimal substrate rigidity for maximum polarization
  - Thick substrate: include nonlocal elasticity → traction penetration length in terms of substrate and cell parameters

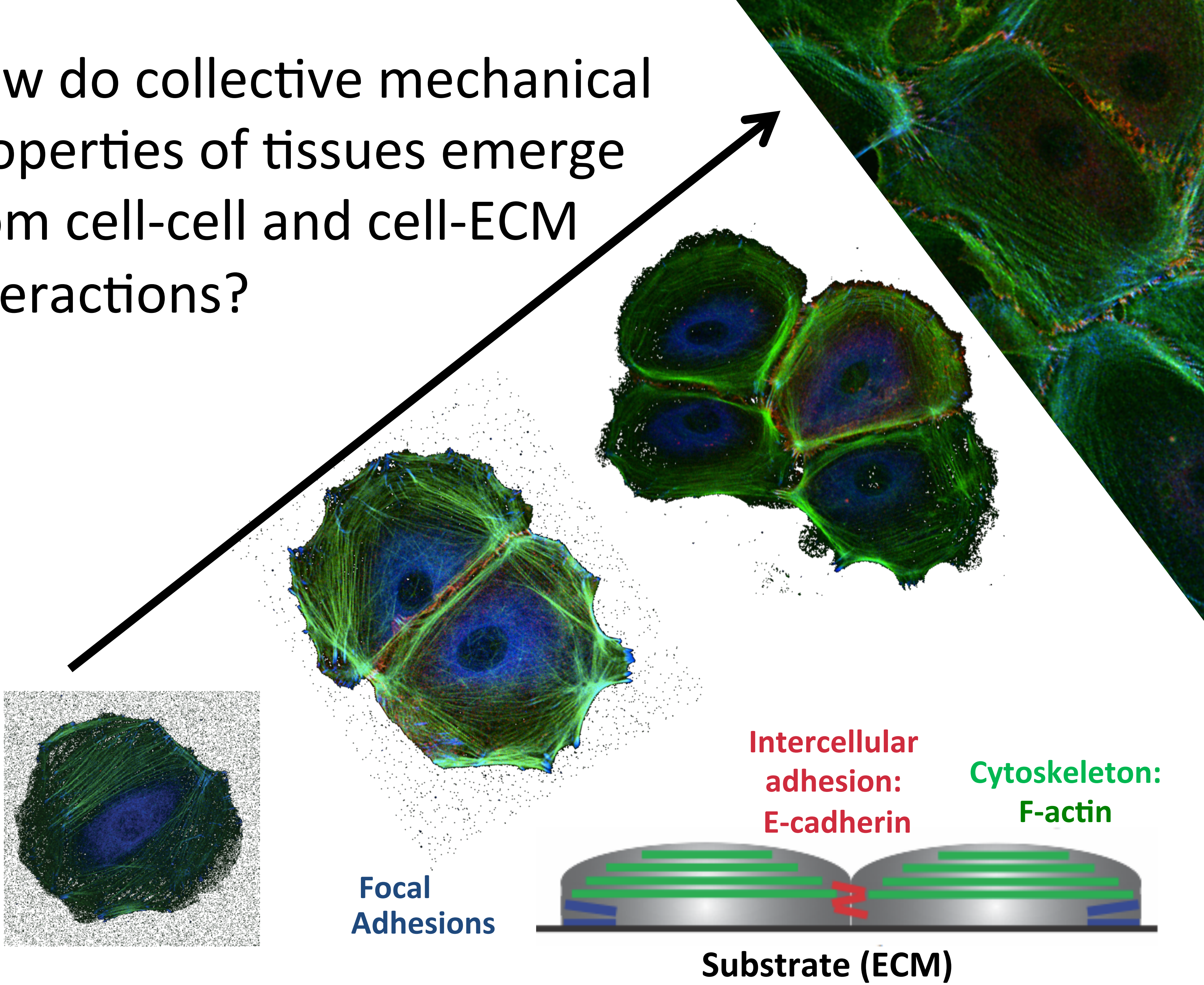


nonlocal elastic response

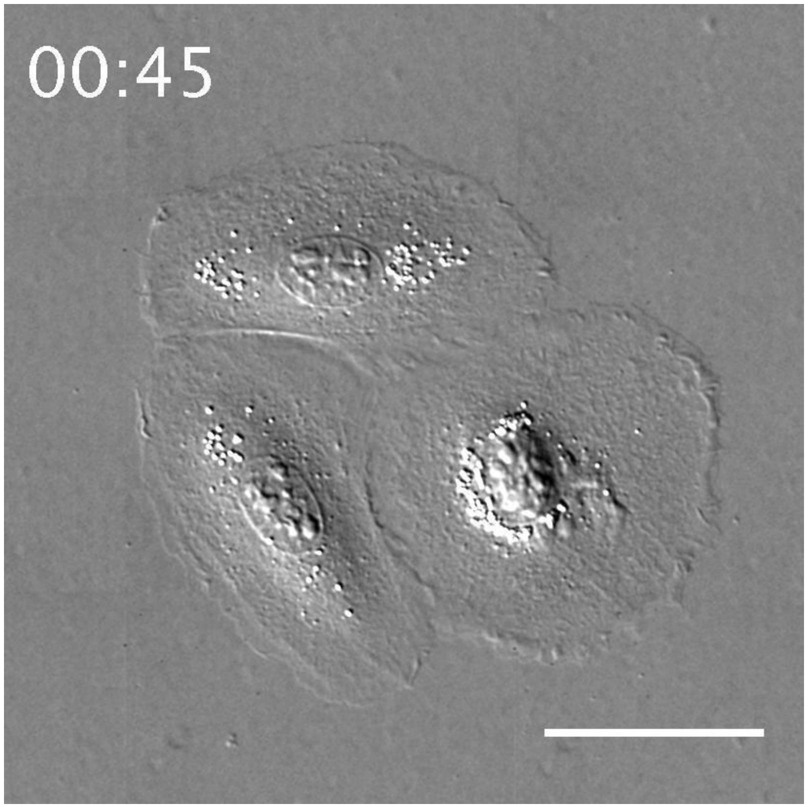
→ cell colonies

Banerjee & MCM, PRL 2012

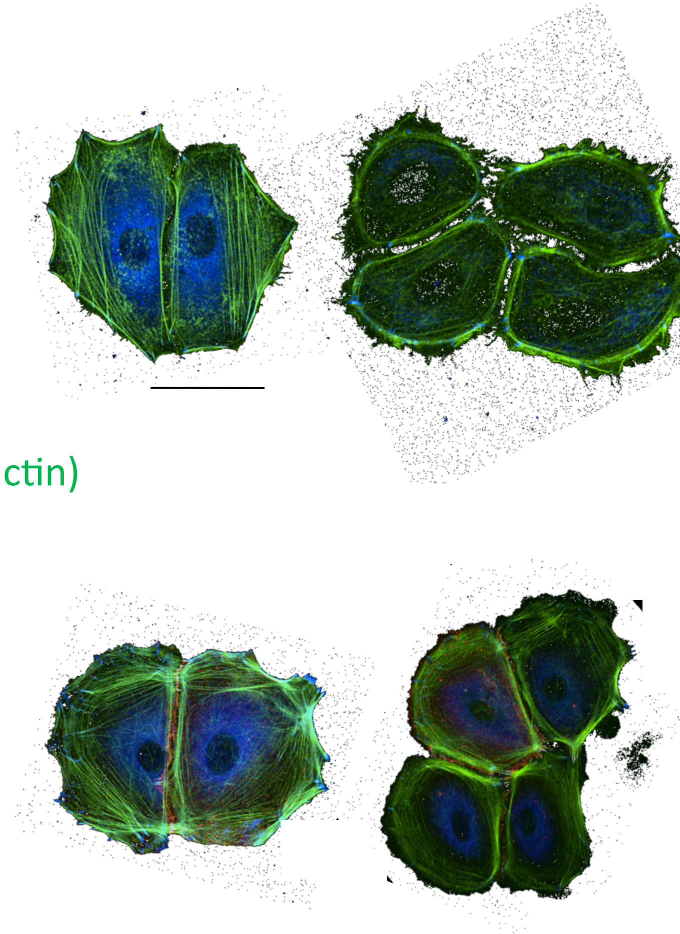
How do collective mechanical properties of tissues emerge from cell-cell and cell-ECM interactions?



Calcium promotes formation of intercellular adhesions



Calcium alters morphology and cohesiveness of colonies

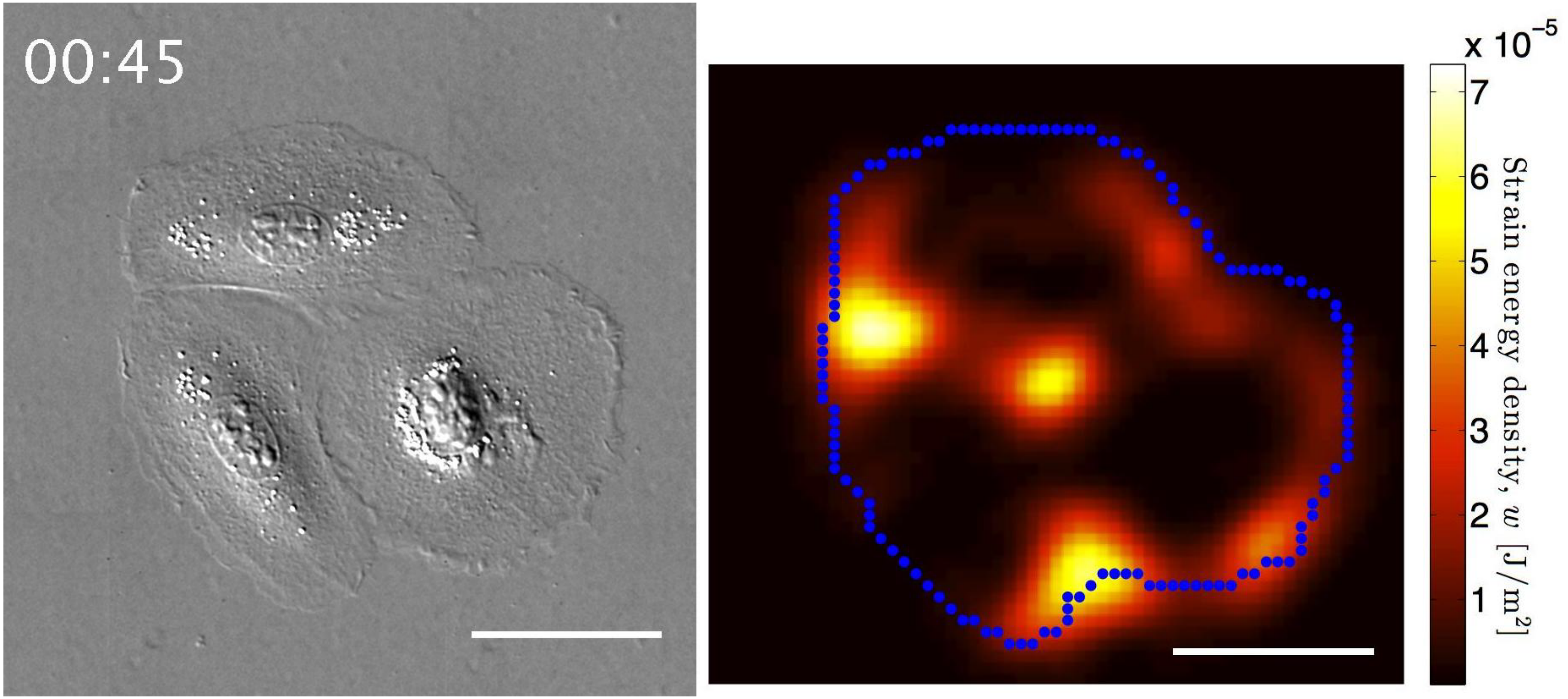


Low calcium

High calcium

Phalloidin (F-actin)
E-cadherin
Zyxin
Scale bars 50 µm

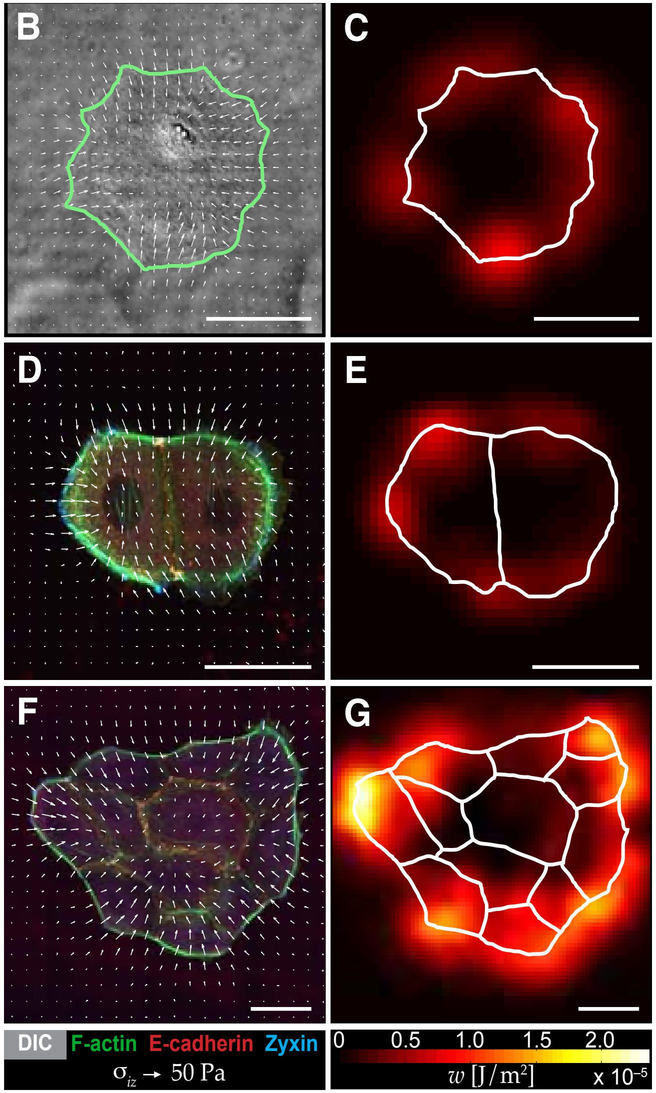
Intercellular adhesions organize Cell-Matrix Traction Forces



A.F. Mertz et al., **PNAS 2013**

Strain Energy and Traction Localization in Keratinocyte colonies

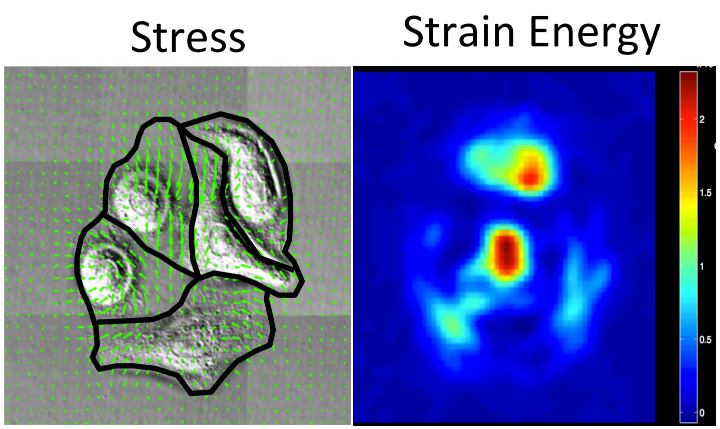
Mertz, Banerjee, Y. Che, G. German, Y. Xu, C. Hyland, MCM, V. Horseley & ER Dufresne, **PRL 2012**



Scale bars 50 µm

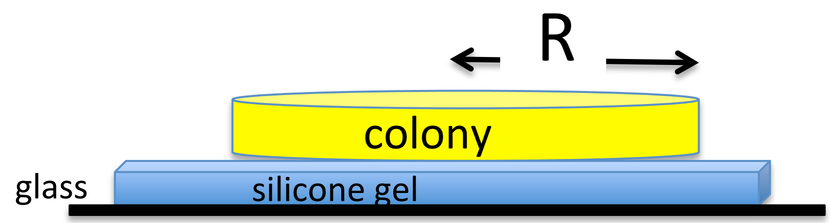
Traction (B,D,F) and strain energies (C,E,G), for single cells (B,C), cell pair (D,E) and 12-cell colony (F,G).

Low-calcium wildtype



Contractile pancake model for adherent cell colonies

- Colony as contractile elastic continuum
- Assume in-plane rotational symmetry.



$$\partial_j \sigma_{ij} = 0 \quad \rightarrow \quad \frac{h}{r}\left[\partial_r (r\bar{\sigma}_{rr}) - \bar{\sigma}_{\theta\theta}\right] = \underbrace{Y u_r(z=0)}_{T_r(r)}$$

$$\bar{\sigma}_{rr}(r=R) = 0$$

$$\sigma_{ij} = \sigma_{ij}^{el} + \sigma_a \delta_{ij}$$

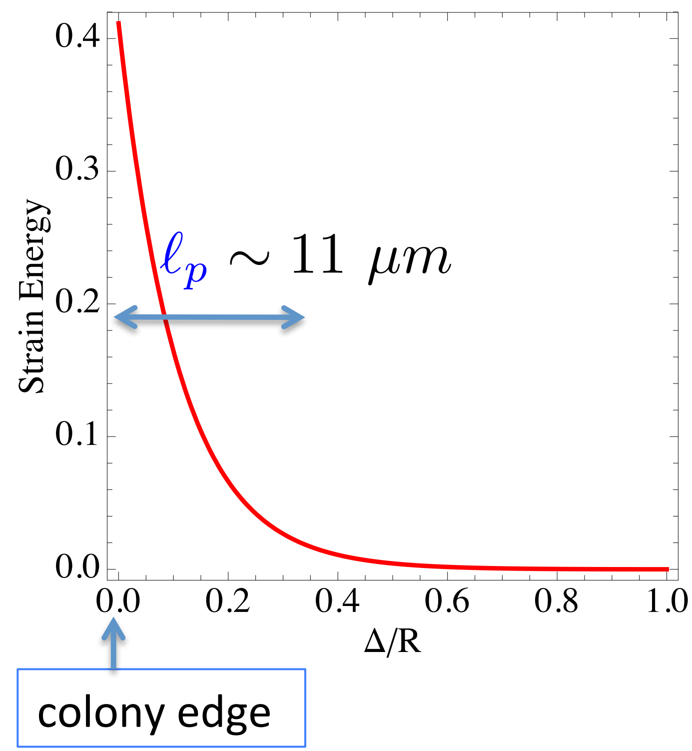
$$\sigma_{ij}^{el} = \delta_{ij}\frac{E\nu}{(1+\nu)(1-2\nu)}\vec{\nabla}\cdot\vec{u} + \frac{E}{2(1+\nu)}(\partial_i u_j + \partial_j u_i)$$

Strain Energy density

$$w(r) \sim \tfrac{1}{2}\vec{T}(\vec{r})\cdot\vec{u}(\vec{r}) = \tfrac{1}{2} Y u_r^2(r)$$

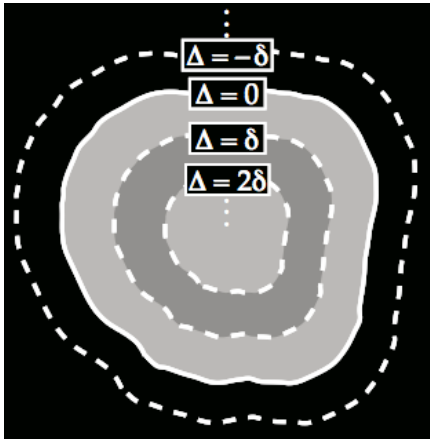
Penetration length:

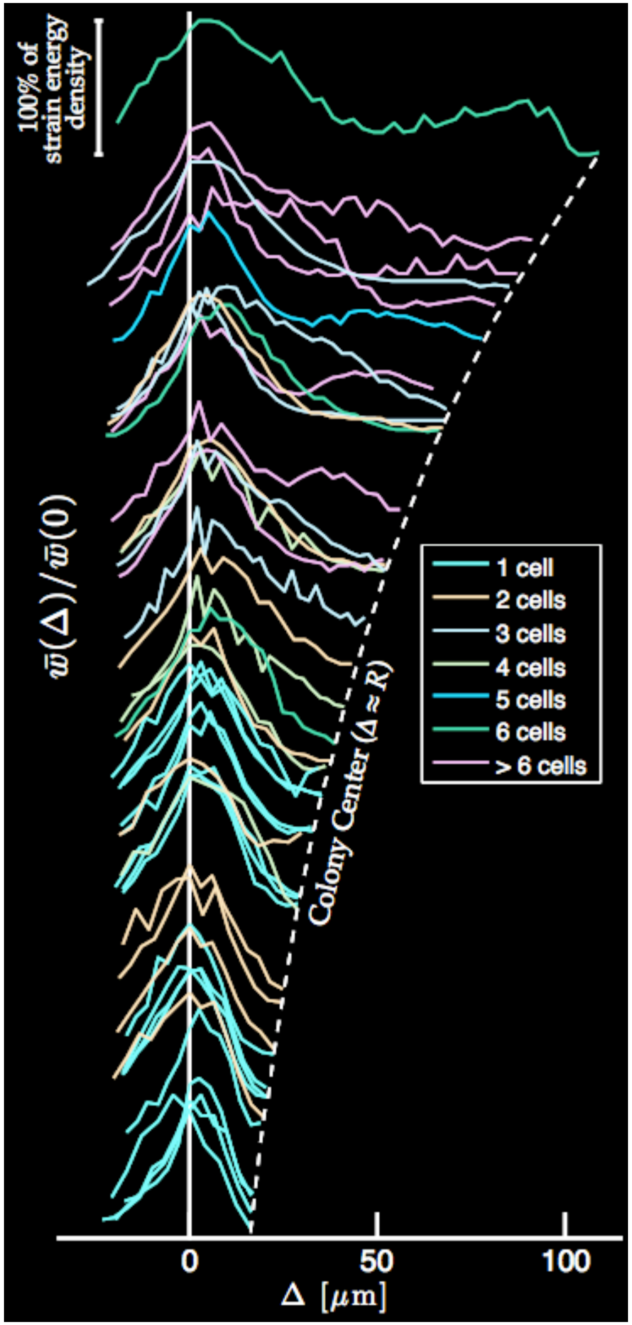
$$\ell_p^2 = \frac{E(1-\nu)h}{Y(1+\nu)(1-2\nu)}$$



45 colonies, 1-27 cells
R: 20-200μm

→ strain energy concentrated at colony periphery

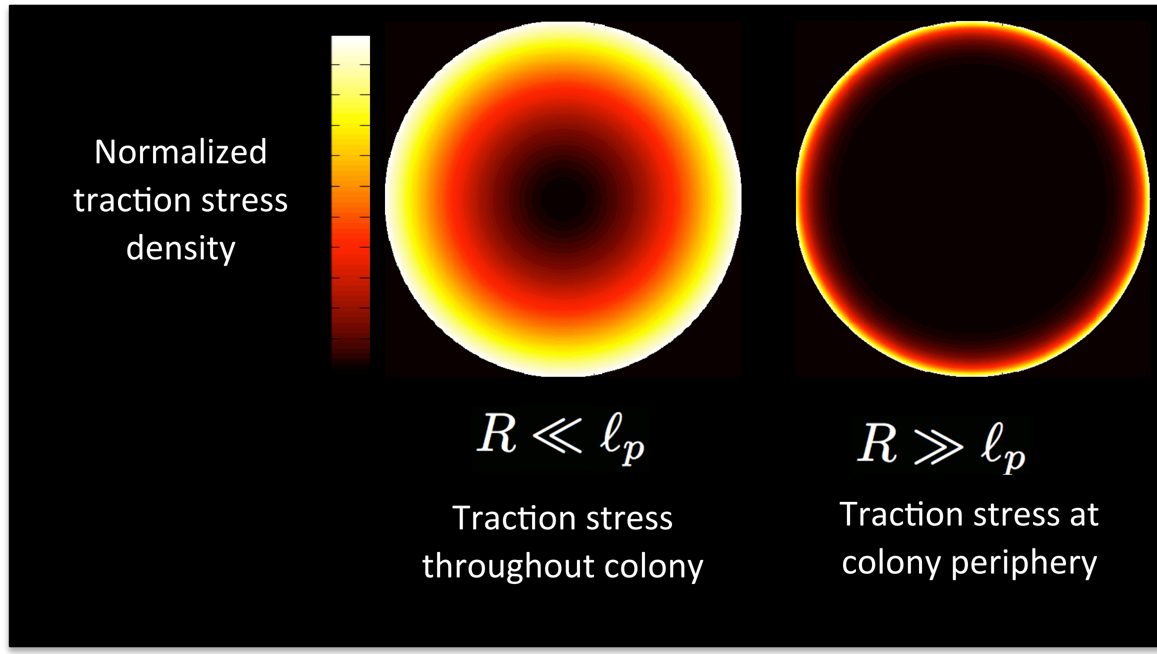




Total traction stress

$$\mathcal{F} = \int dA \sqrt{(\sigma^s_{xz})^2 + (\sigma^s_{yz})^2}$$

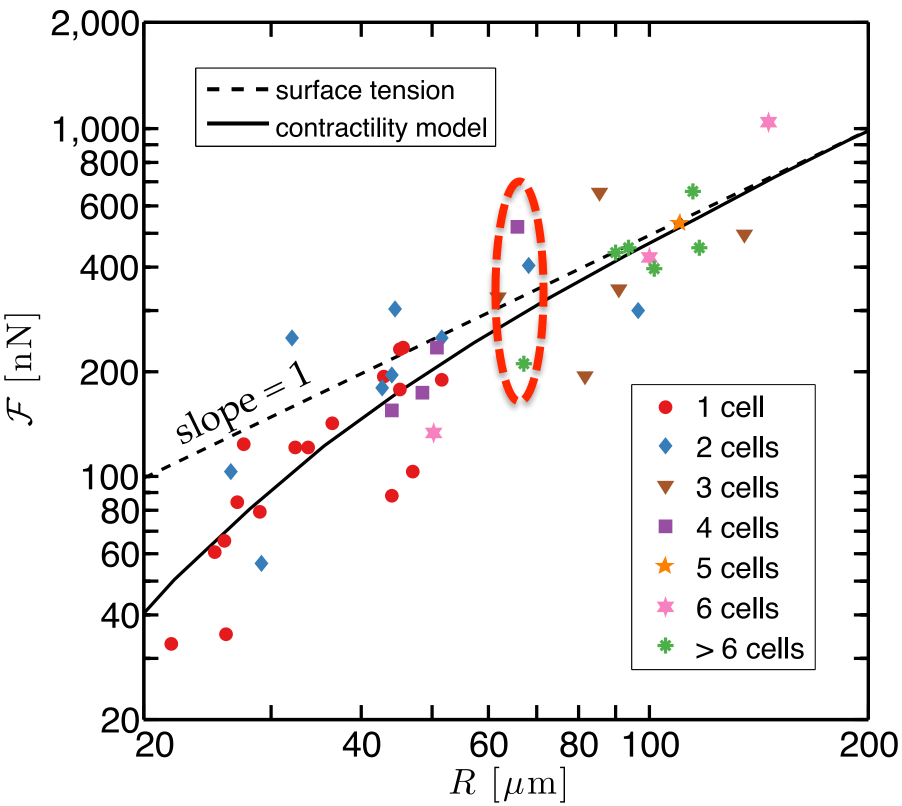
$$= 2\pi Y \int_0^R dr\ r\ u_r(r)$$



$$\ell_p \ll R \qquad \mathcal{F}(R) \propto R^3$$

$$\ell_p \gg R \qquad \mathcal{F}(R) \simeq 2\pi h \sigma_a R \propto R$$

Scaling of Traction Forces with colony radius



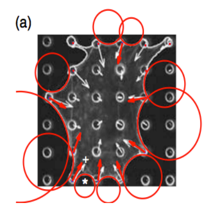
Mertz, Banerjee *et al.*, PRL 2012

Large colonies appear to behave like liquid droplets wetting a surface !

- **Total traction** grows monotonically with **colony radius** and **not** the number of cells.
- Linear scaling at large colony radius suggests emergence of an ***effective surface tension*** originating from contractility.

$$\frac{\mathcal{F}(R)}{2\pi R} \simeq h\sigma_a \simeq (8 \pm 2) \times 10^{-4}\, N/m$$

Micropillars

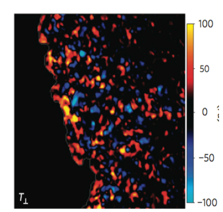


Single HUVEC

$\gamma \approx 2 \times 10^{-3}$ N/m

Bischofs *et al.*, Physical Review Letters, 2009, expanding on Lemmon *et al.*, Mechanics & Chemistry of Biosystems, 2005

Flat elastic substrate



Sheet of MDCK epithelial cells

$\gamma \approx 7 \times 10^{-4}$ N/m

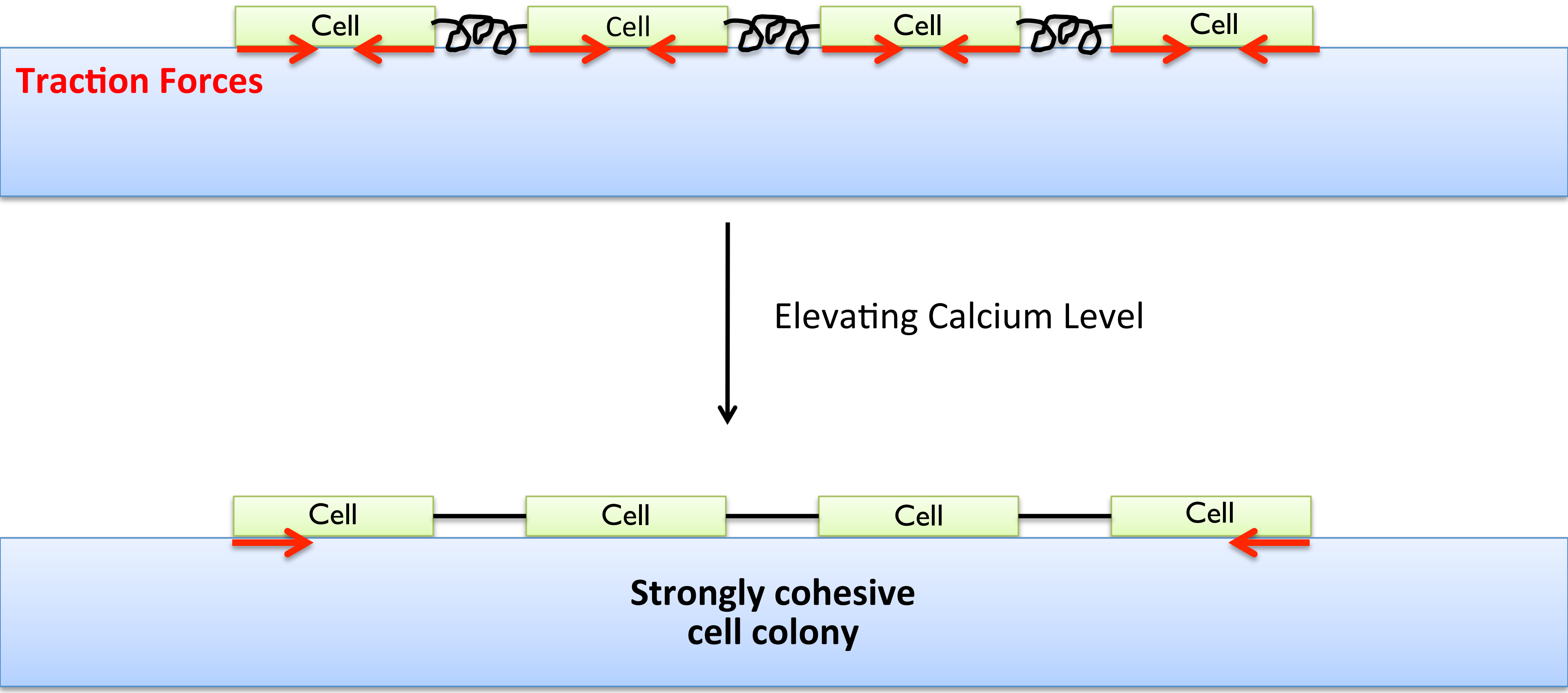
adapted from Trepat *et al.*, Nature Physics, 2009

$$\left.\begin{array}{r}\text{surface tension} \sim h\sigma_a \sim 8\times 10^{-4} N/m \\ h \simeq 0.2\mu m\end{array}\right\} \rightarrow \sigma_a \simeq 4kPa$$

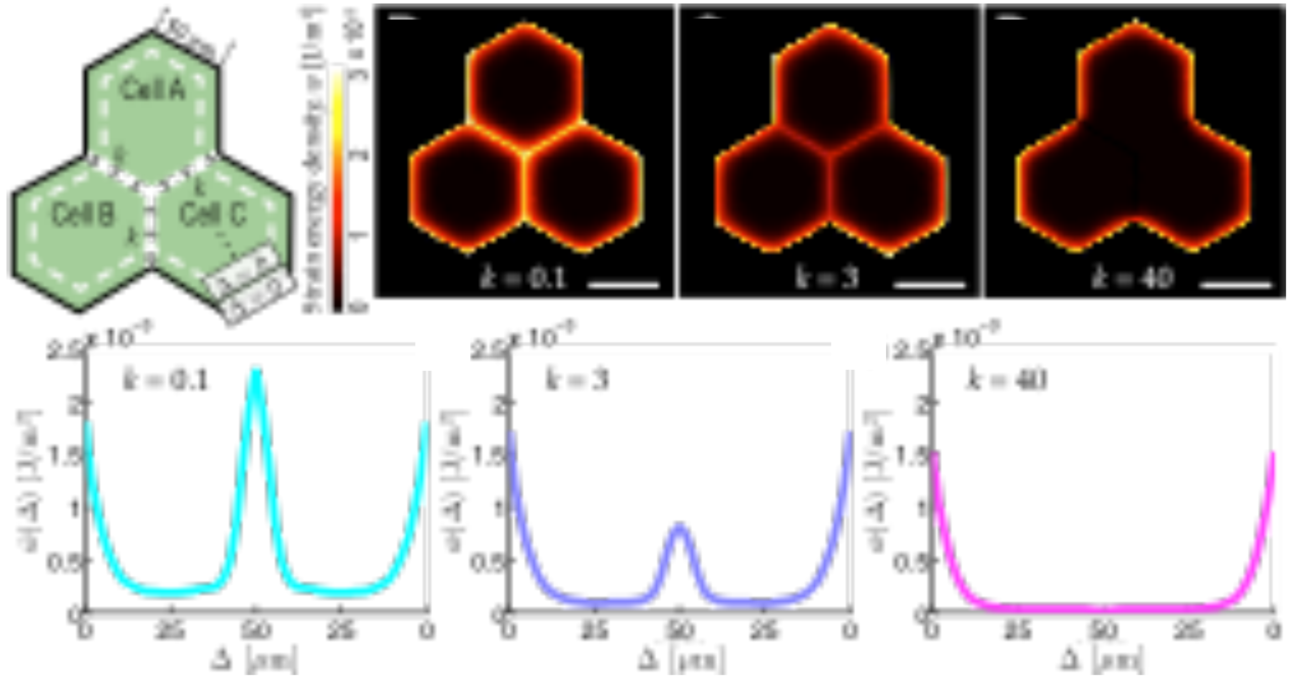
$$\sigma_a \sim \rho_m k_m \Delta_m \sim 1kPa \qquad \begin{cases}\rho_m \sim 10^3 \mu m^{-2} & \text{density of bound myosins} \\ k_m \sim 1pN/nm & \text{motor stiffness} \\ \Delta_m \sim 1nm & \text{motor stretch}\end{cases}$$

Cell-cell adhesion as an elastic bond

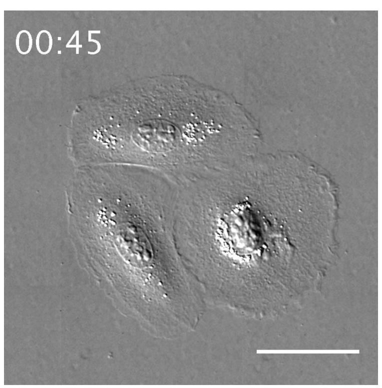
Cells adhere to each other via hookean springs with adjustable stiffness

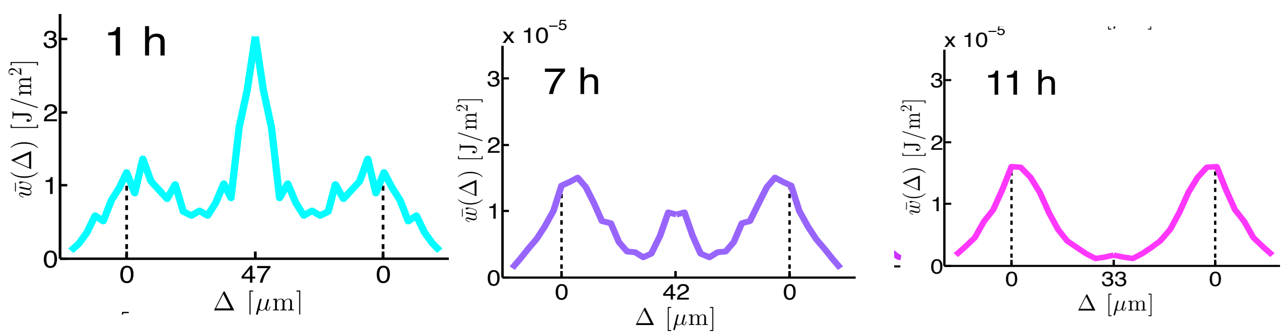


2D model with shapes and springs captures experimental data



increasing stiffness of cell-cell springs





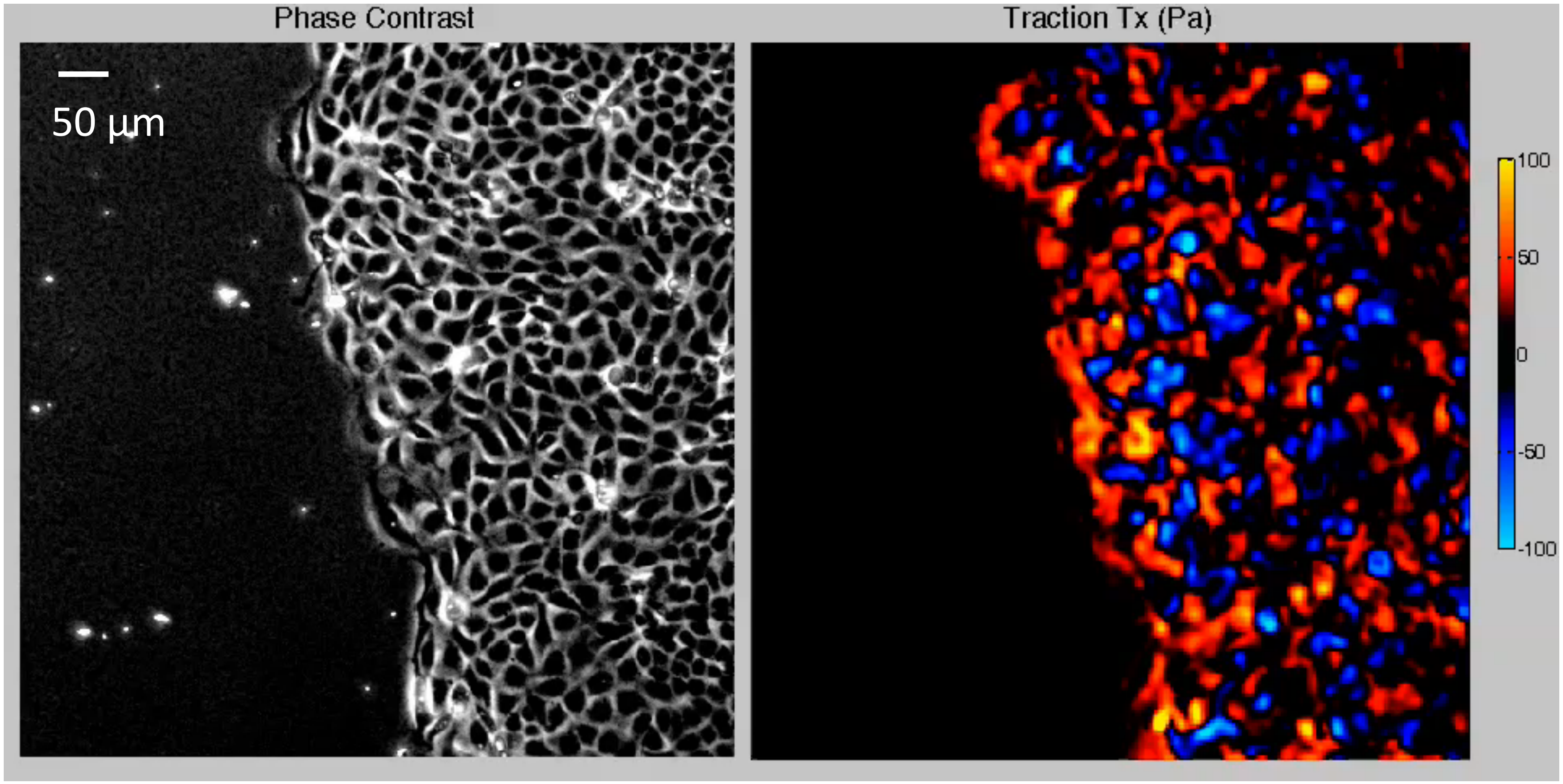
time after Ca^{2+} addition

Mertz, Che, Banerjee *et al.*, PNAS, 2013

Adherent cells: Summary & Questions

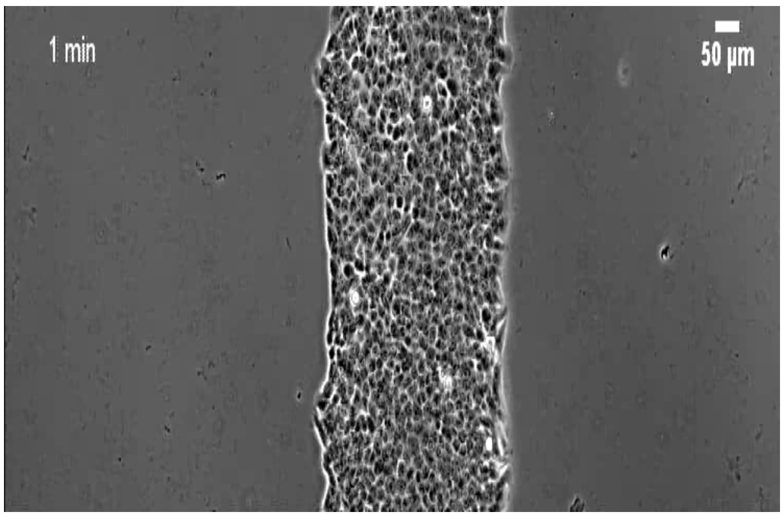
- Cohesive adherent cell colony as an elastic contractile continuum
- Mechanical output of cell colony does not depend on number of cells, but only on geometrical size of colony
- Experiments and physical model show emergence of surface tension in large colonies
- How do cell colonies and tissues actively regulate surface tension – contractility vs. cohesiveness?
- What is the connection between measured surface tensions of 2D colonies and 3D aggregates? (Guevorkian et al 2010, Manning et al. 2010, …)
- Can cell colonies be thought of as wetted droplets?

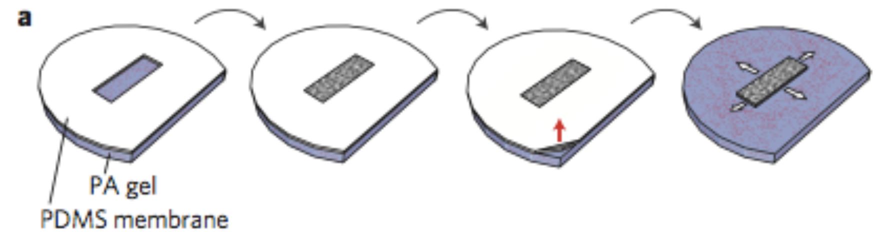
Collective Cell Migration



Trepat et al, Nature Physics (2009).
MDCK cells on polycrylamide gel of elastic modulus 1250Pa.

Collective migration of cell monolayers is important in many biological processes such as wound repair, morphogenesis and cancer invasion





Continuum models can account for some experimental findings, including the existence of travelling mechanical waves that control stress propagation

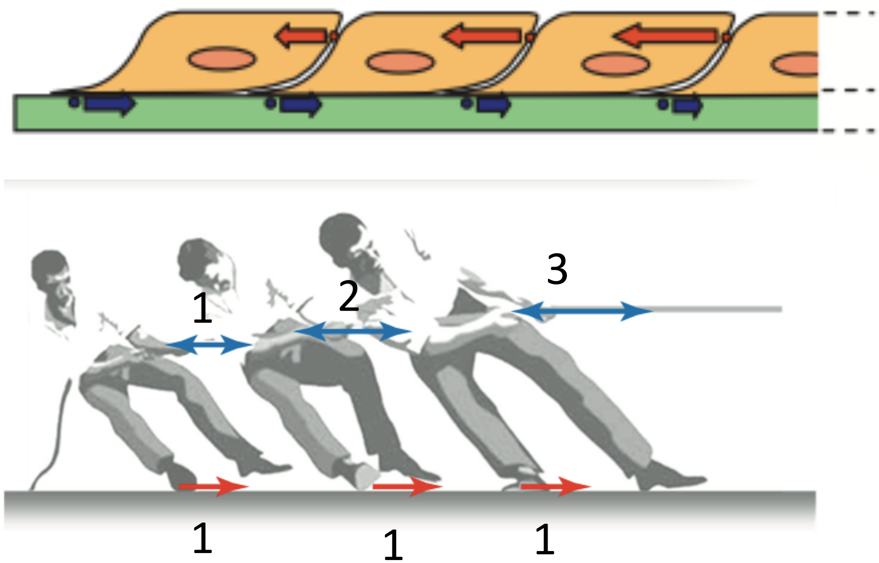
X. Serra-Picamal et al., Nature 2012

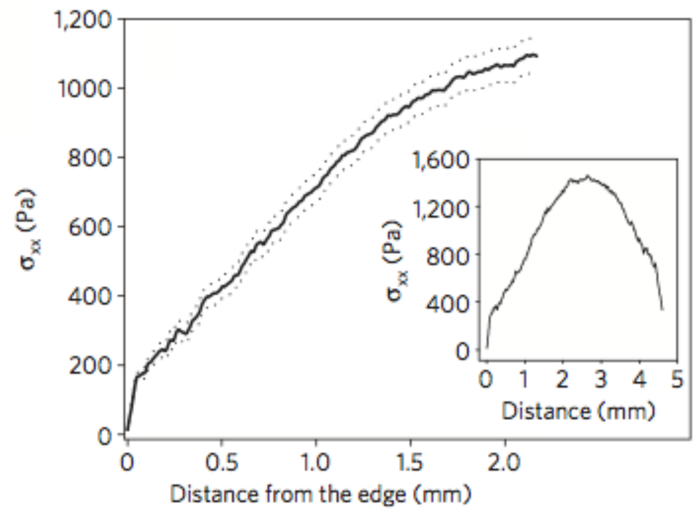
- Salm & Pismen, Phys. Biol. 2012
- Köpf & Pismen, Soft Matter & Physica D 2013
- Sepúlveda et al., PLoS Comput Biol 2013

- Basan et al PNAS 2012
- Arciero et al., Biophys J. 2011
- …

Experimental Finding

- Build-up of tensile stresses in cell layer.
- Cells pull on neighbors → collective migration





Tug of war: forces are balanced!
Traction gives intercellular stresses

MDCK epithelial cells

Trepat et al, Nat Phys 2009

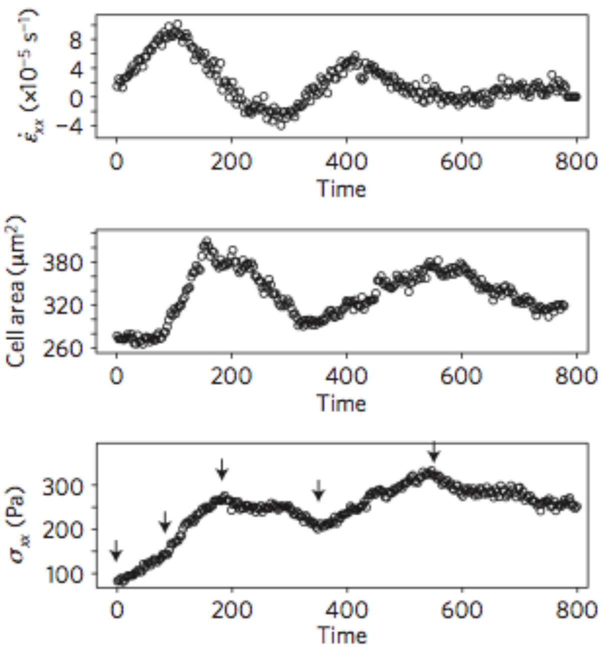
Experimental Finding

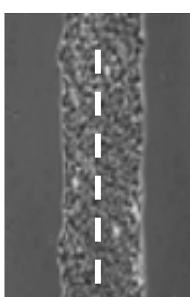
Serra-Picamal et al., Nature 2012

strain rate

area strain

stress





Liquid:

$$\sigma = \eta \partial_x v$$

$\partial_x v$ strain rate

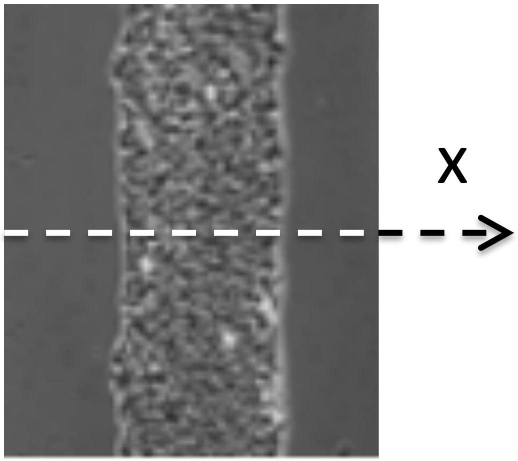
Solid:

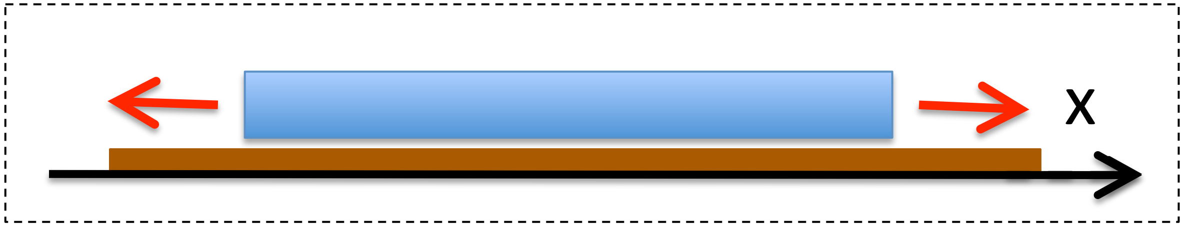
$$\sigma = \mu \partial_x u$$

$\partial_x u$ strain

Stress at the monolayer midline oscillates in time, in phase with cell area and out of phase with strain rate → elastic behavior

Spreading cell layer (2d)





- Displacement **u**(x)
- Polarization **P**(x)
- Overdamped dynamics

$$\Gamma \partial_t u_i = \partial_j \sigma_{ij} + f_0(\Delta\mu) p_i$$

$$\partial_t p_i = -[a + b\mathbf{p}^2] p_i + K \nabla^2 p_i - \beta \partial_j u_{ij}$$

$$\sigma_{ij} = \sigma_{ij}^{el} + \sigma_{ij}^{a} \qquad \sigma_{ij}^{a} = \zeta \Delta\mu \delta_{ij} + \zeta' \Delta\mu \, p_i p_j$$

$$\zeta \Delta\mu = \sigma_a$$

$$\zeta' \Delta\mu = \alpha$$

Forces are always balanced

$$\Gamma \partial_t u_i = \partial_j \sigma_{ij} + f_0 p_i$$

Spreading or propulsion force

$$\partial_i \sigma_{ij} = \Gamma \partial_t u_i - f_0 p_i = T_i(x)$$

$$\int dx T(x) = 0$$

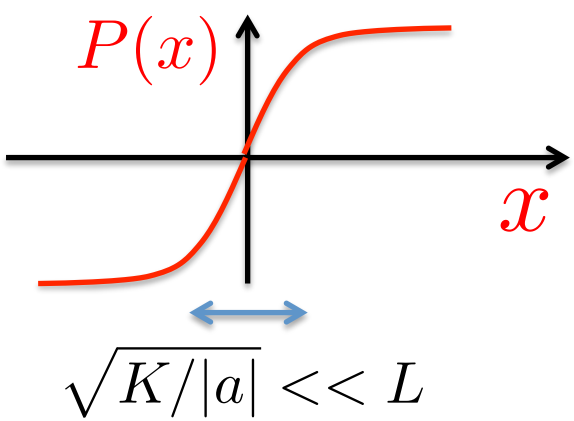
Spreading cell layer: $p_x(0) = -p_0 \quad p_x(L) = +p_0$

$$\sigma(0) = \sigma(L) = 0$$

Neglect dynamics of polarization

Deep in the polarized state we can assume that layer polarization relaxes fast compared to time scale of stress propagation to the steady state profile that minimizes *F*

$$\partial_t p_i = -[a + b\mathbf{p}^2]p_i + K\nabla^2 p_i = 0$$



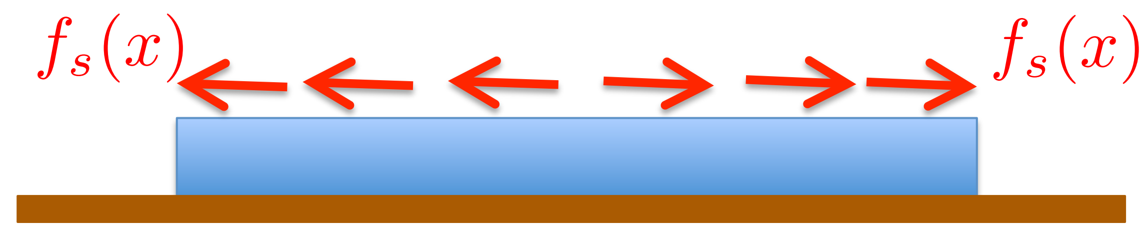
$$P(-L/2) = -P_0$$

$$P(+L/2) = +P_0$$

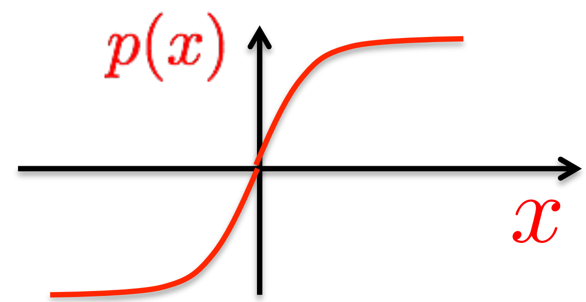
$$P_0 = \sqrt{-a/b}$$

Mechano-chemical coupling

c(x): ATP concentration



spreading force: $f_s(x) \sim \Delta\mu \, p(x)$



$$\Gamma \partial_t u = f_s(x) + \partial_x \sigma$$

$$\sigma = B \partial_x u + \zeta \ln(c/c_0)$$

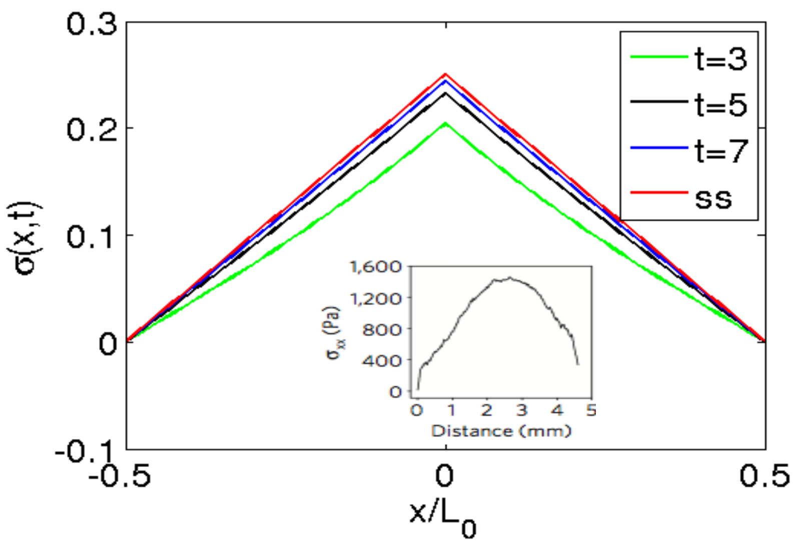
$$\Delta\mu \sim \ln(c/c_0)$$

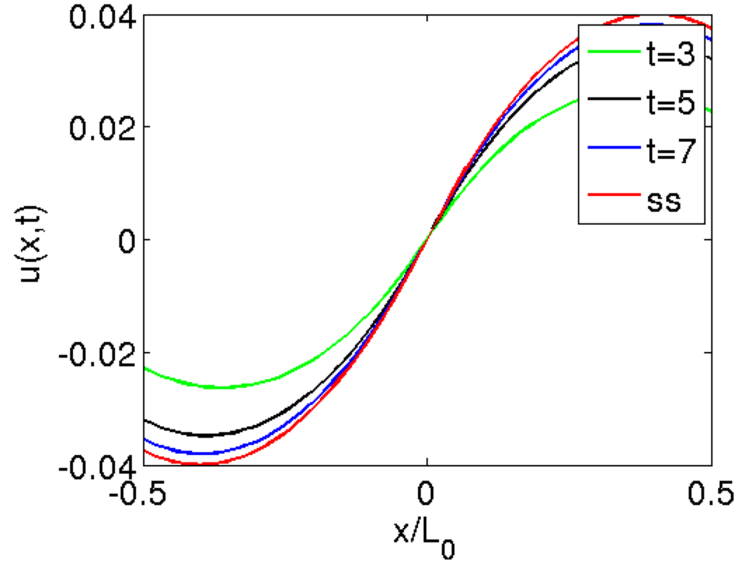
$$\partial_t c + \partial_x (c\dot{u}) = -\gamma(c - c_s) + D\partial_x^2 c - \beta \partial_x u$$

- Salm & Pismen, Phys. Biol. 2012
- Köpf & Pismen, Soft Matter & Physica D 2013

Fast excess ATP relaxation: $t >> 1/\gamma$

$$\Gamma\partial_t u = f_s(x) + B_{eff}\partial_x^2 u \qquad B_{eff} = B - \zeta\beta/\gamma$$



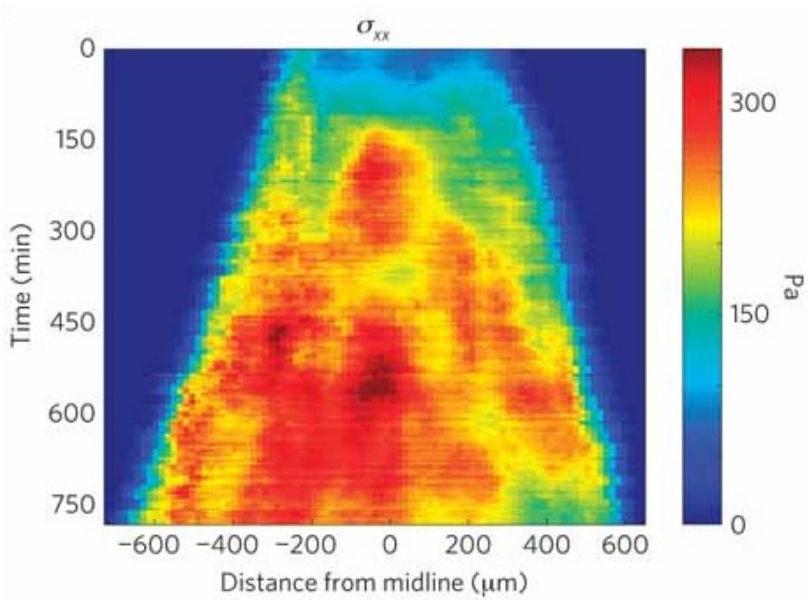


Cell layer spread diffusively for

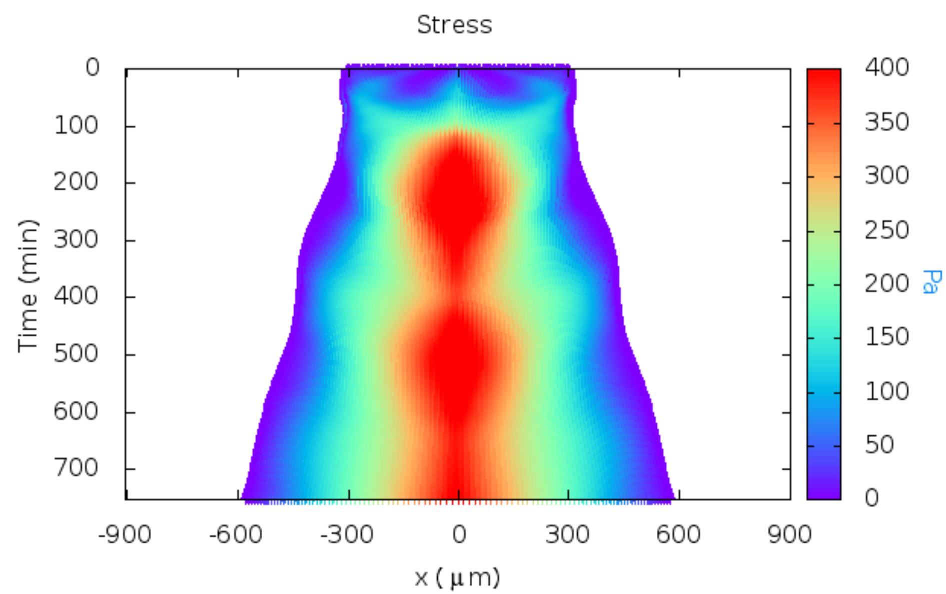
$$f_s > f_s^* = 8\beta(c_s - c_0)$$

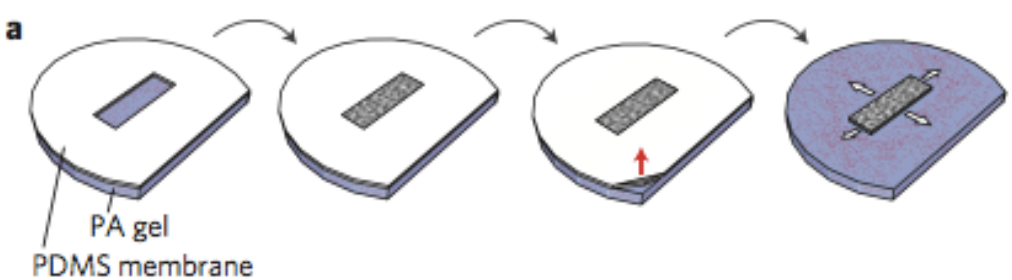
ATP dynamics → Propagating Stress Waves

Experiments



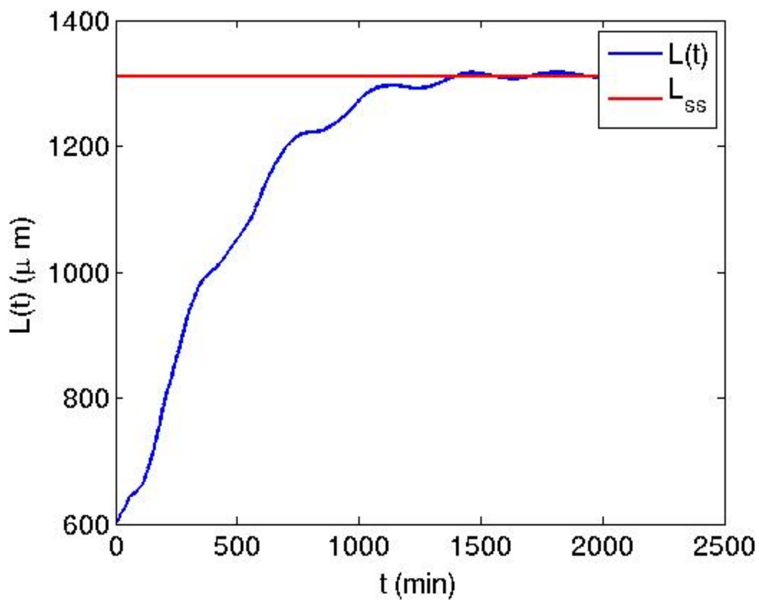
Contractile layer model



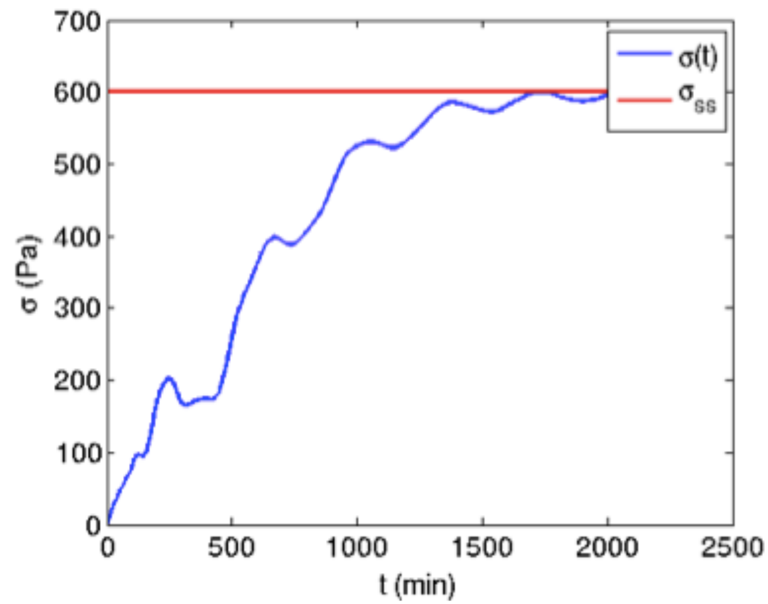


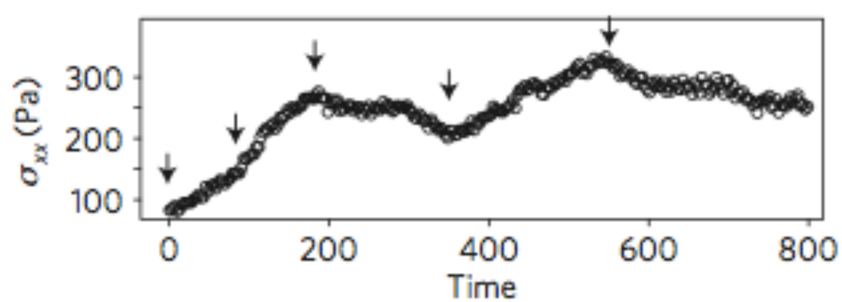
X. Serra-Picamal et al., Nature 2012

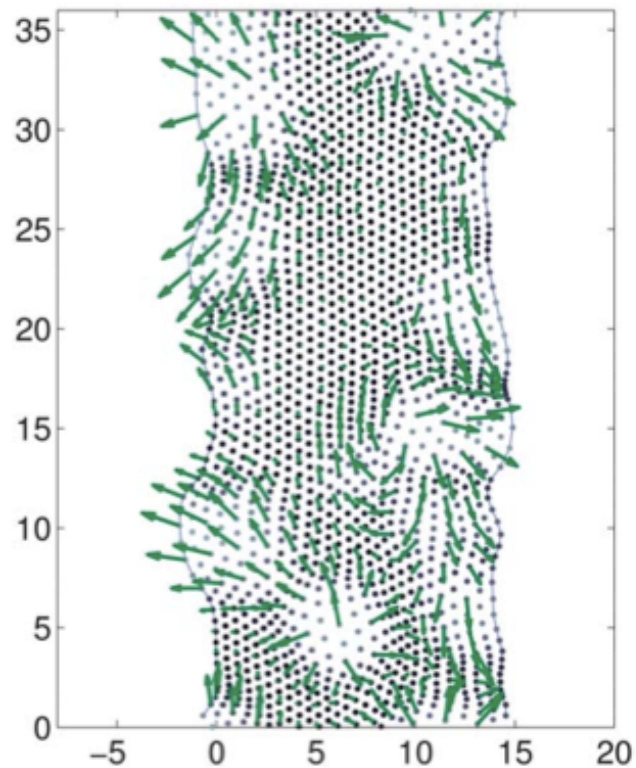
Cell layer width vs time



Midline stress vs time

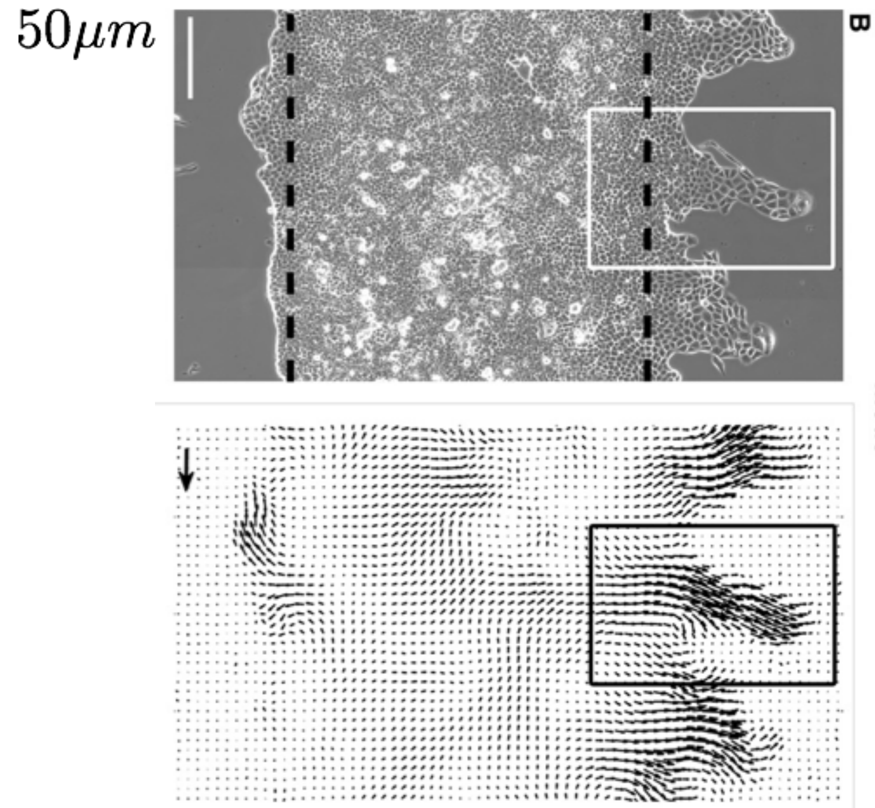






Köpf & Pismen, Soft Matter 2013

But requires ``wetting force’’



Petijean et al, Biophys. J. 2010, MDCK cells

Cells & Tissues as Active Matter

Single Cells

- *Global mechanics:*
  - Minimal continuum models provide understanding of force transmission to environment
  - spatial distribution of contractility and focal adhesion has little effect on stress and traction distribution
- *Local Mechanics*: Traction stresses are highly sensitive to substrate stiffness, cell shape or adhesion geometry.

Cell Colonies

- Cohesive cell colonies wet the substrate underneath with an effective surface tension.
- Colony surface tension emerges from strong intercellular adhesions and acto-myosin contractility.
- Cadherin based adhesions organize cell-matrix forces to the periphery of the colony.