An introduction to soft active matter

through some examples from cell and tissue mechanics

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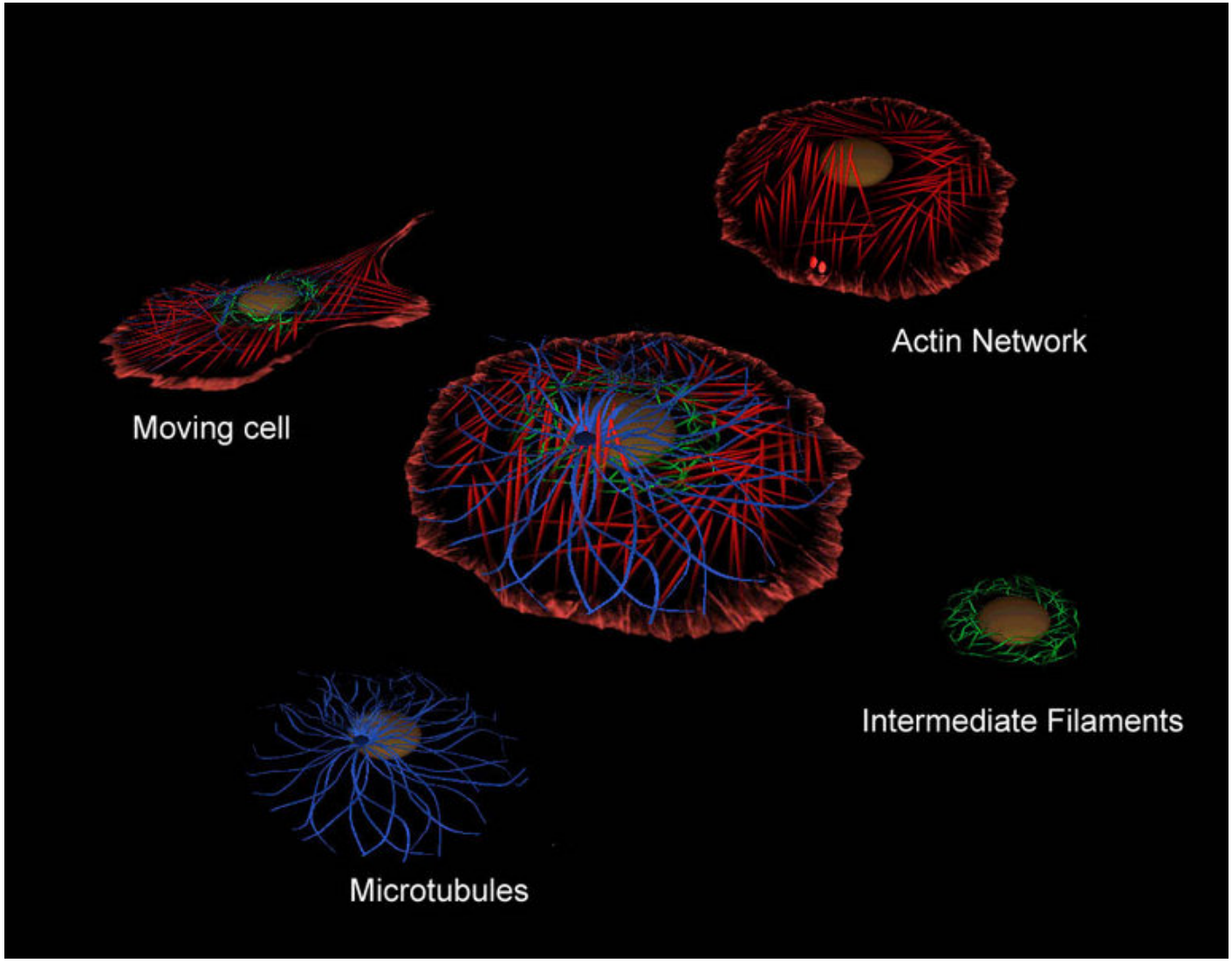
Outline

1. Active polymers

2. Soft and active cells
   - Contractility
   - Contractile actomyosin bundles
   - Lamellipodial motility
   - Polarity patterns

3. Soft and active tissues
   - Cellular aggregates
   - Epithelization of model circular wounds
   - Collective migration of a proliferating epithelium

Cytoskeletal polymers

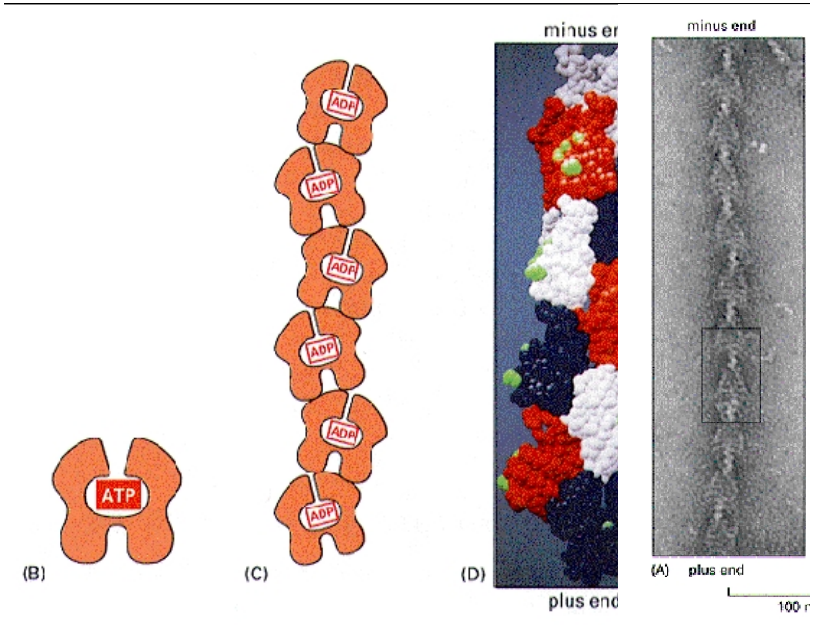


Actin

G-Actin: monomers

- molecular weight $45kDa$
- size $\delta = 5.5$nm
- ATP binding pocket
- polar monomer

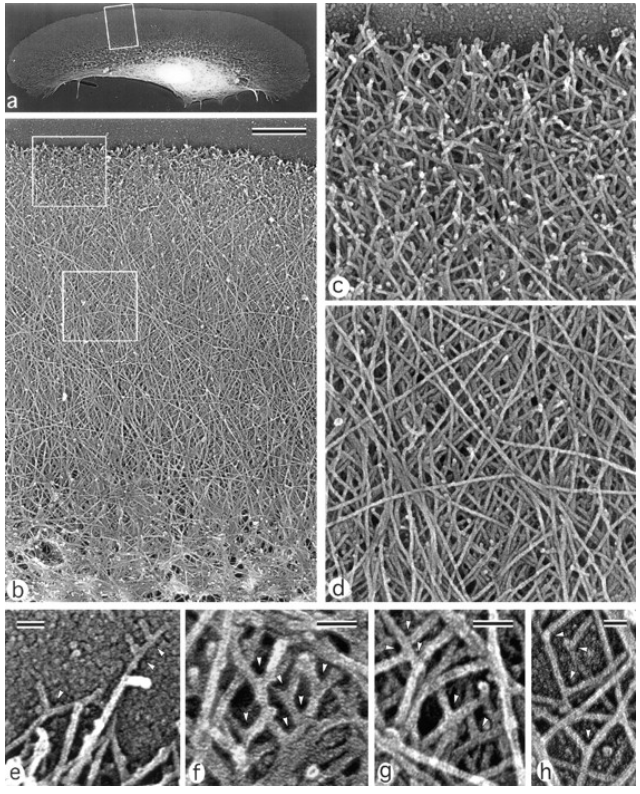
F-Actin: polymers



- 2 protofilaments
- right-handed helix
- 72nm pitch
- 24 monomers per turn

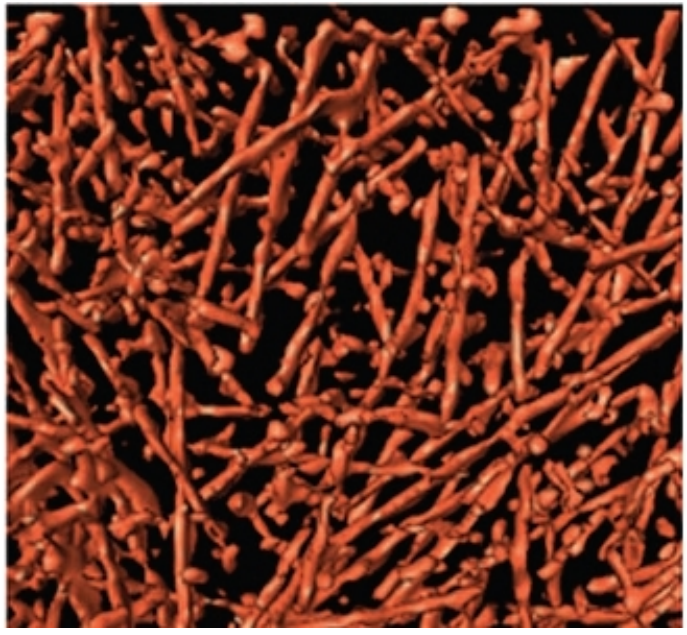
Actin cytoskeleton

Electron microscopy G. Borisy



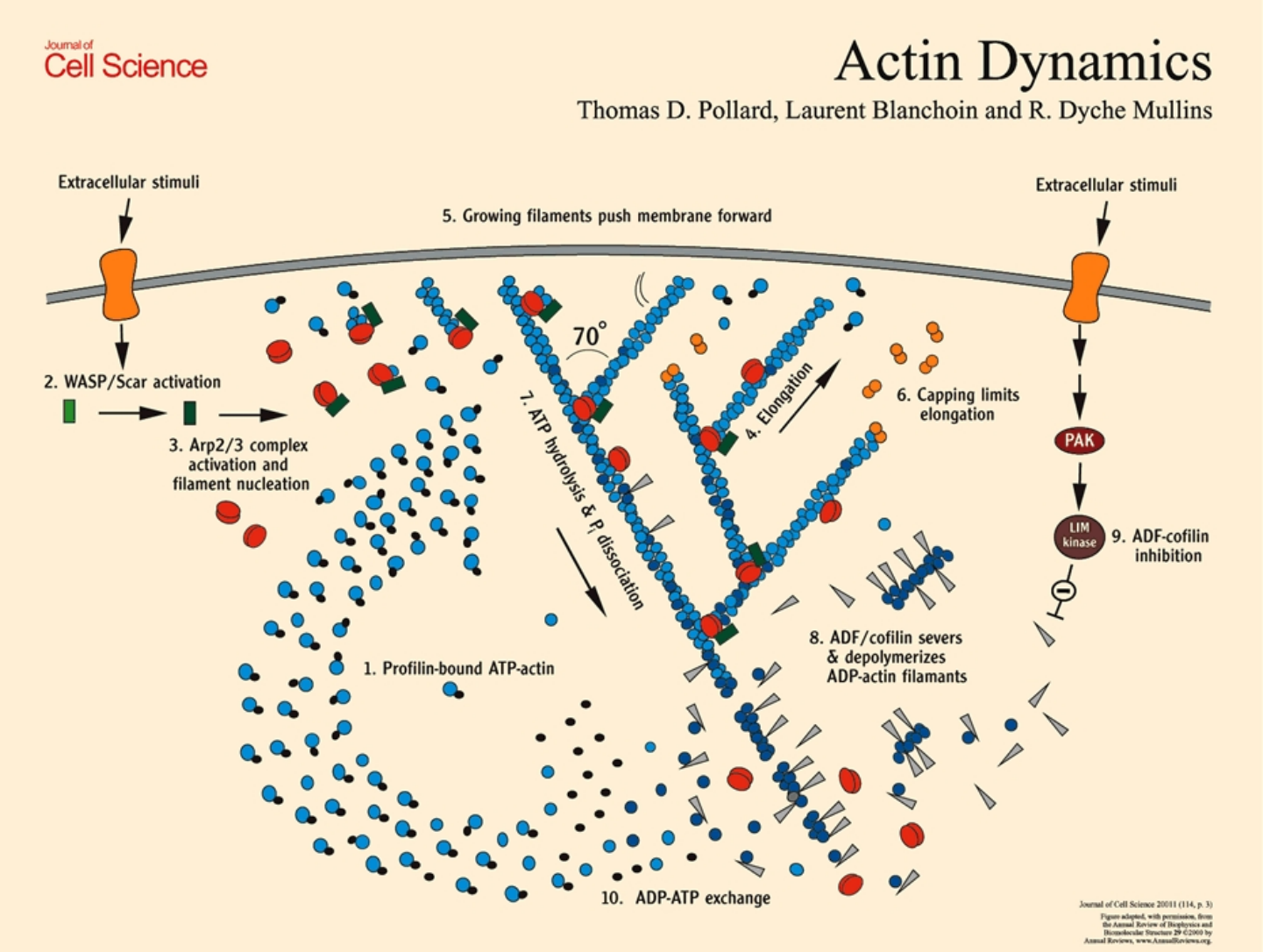
- Fish keratocyte
- Lamellipodium
- Mesh size 50 nm

Cryoelectron tomography W. Baumeister



- Dictyostelium discoideum
- Network of branched and crosslinked filaments

Actin-binding proteins



Outline

Molecular motors (I)

Myosin II

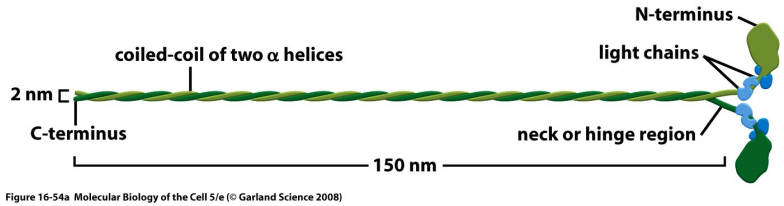
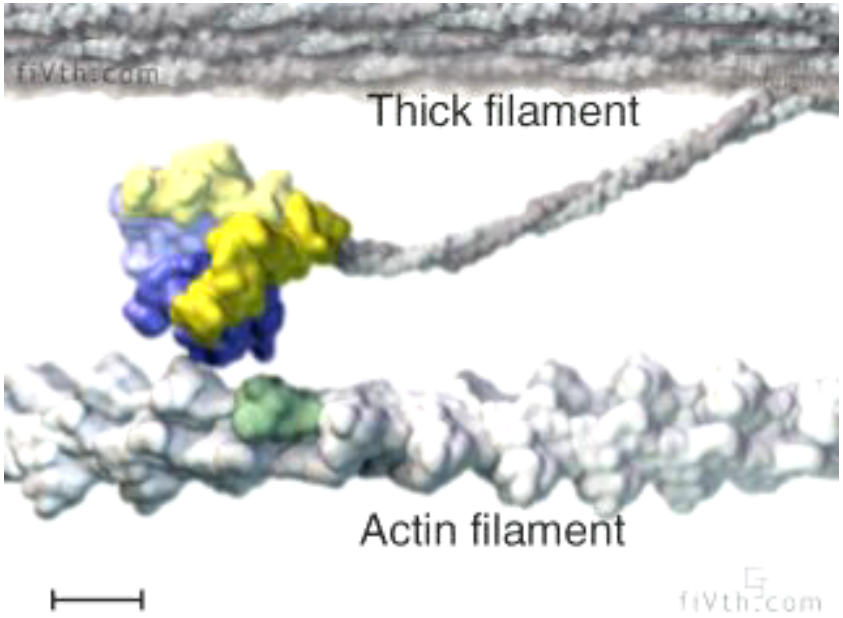


Figure 16-54a Molecular Biology of the Cell 5/e (© Garland Science 2008)

- molecular weight 520 kDa
- size 150nm
- two-headed
- binds ATP and actin

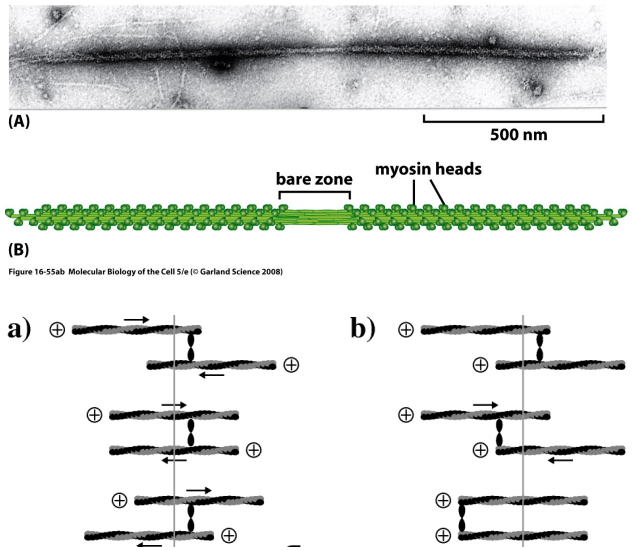
Walking on actin R. Vale



- Fuel: ATP hydrolysis
- Motion towards barbed end

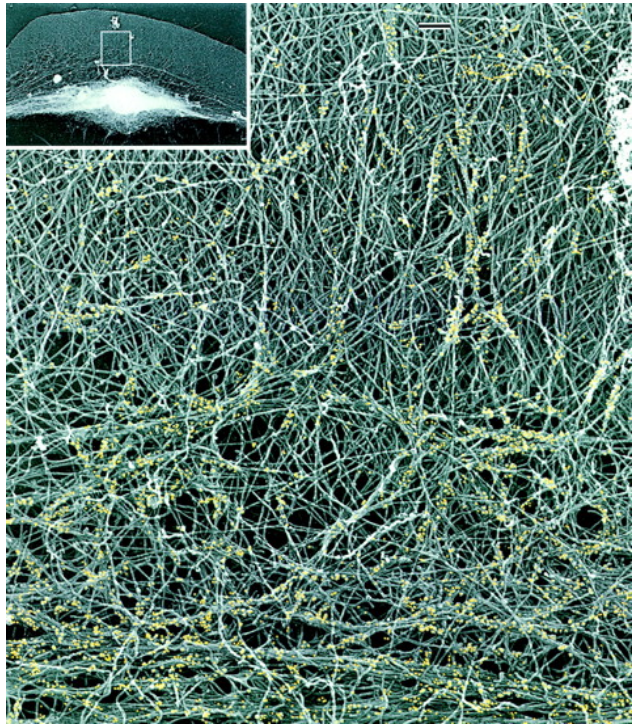
Molecular motors (II)

Bipolar myosin filament



Contraction: adjacent F-actin moved by myosin filaments

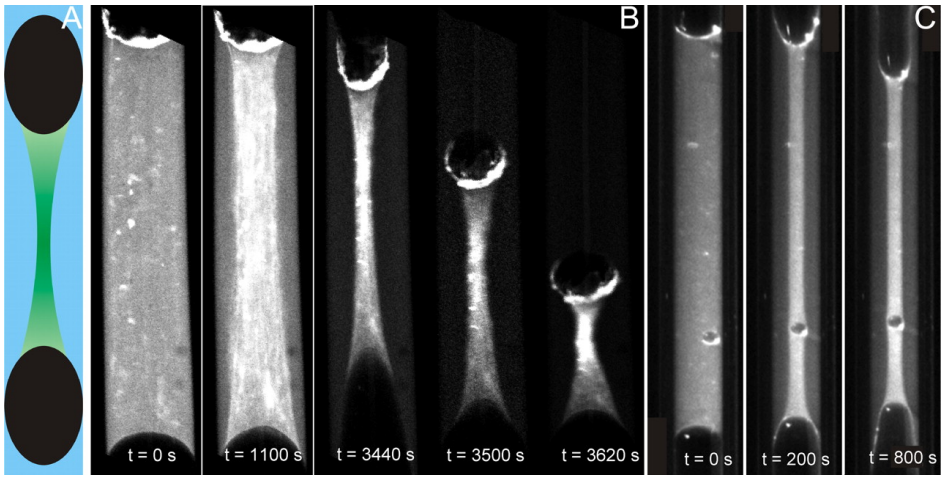
Lamellipodium G. Borisy



Immunogold labeling
Contraction: stress in the gel

In vitro active gels

Actin Myosin α-Actinin gel

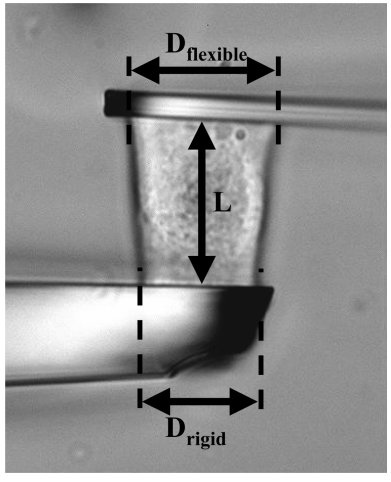


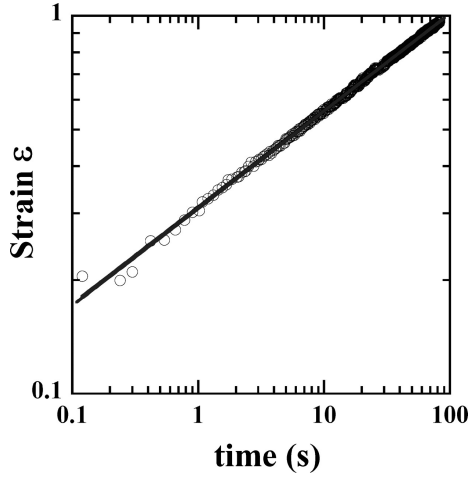
- Actin myosin α-actinin gel in a $400\mu m$ diameter capillary
- ATP introduced at time $t = 0$

Bendix et al., Biophys. J. (2008)

Single cell rheology

Creep measurement





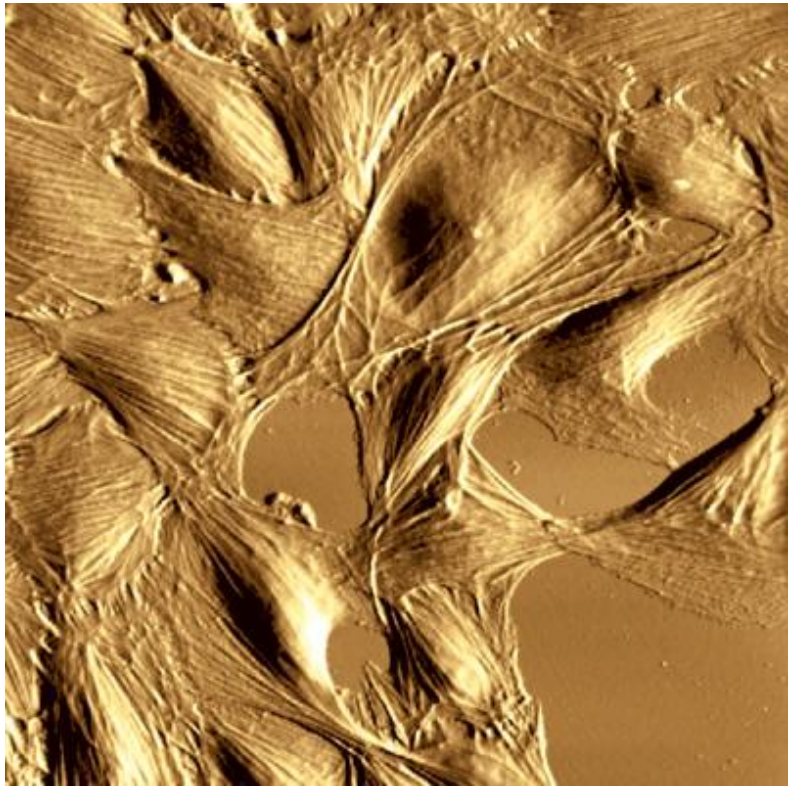
- Weak power law increase of creep $J(t) \sim t^{\alpha}$, $\alpha \approx 0.2$
- Complex elastic modulus $G(\omega) \sim \omega^{\alpha}$
- Large distribution of relaxation times

Here: simplified rheologies

Balland et al., Phys. Rev. E (2006)

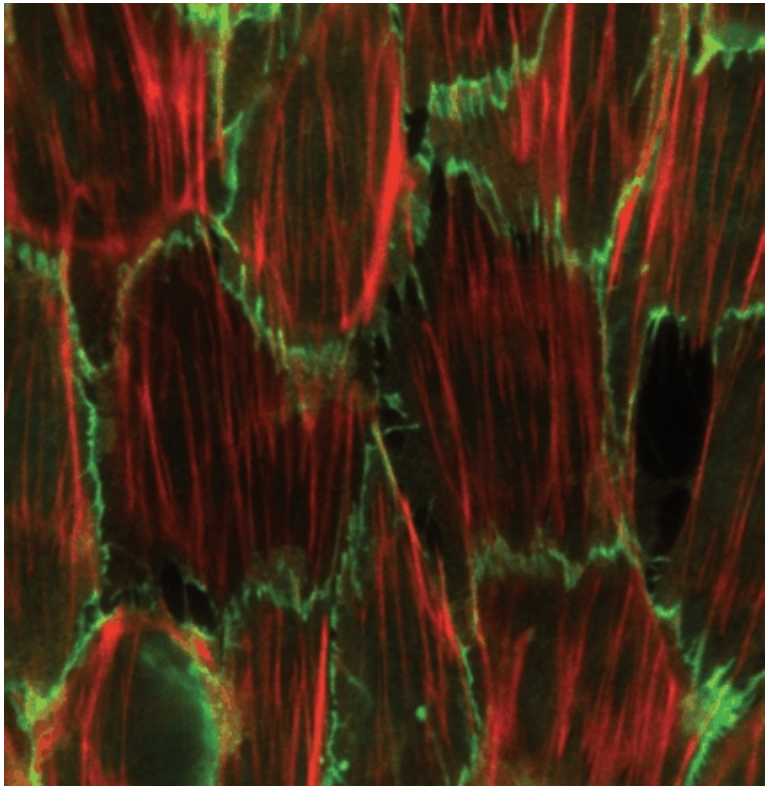
Outline

Contractile actomyosin bundles



Fibroblasts

Swiss Nanoscience Institute

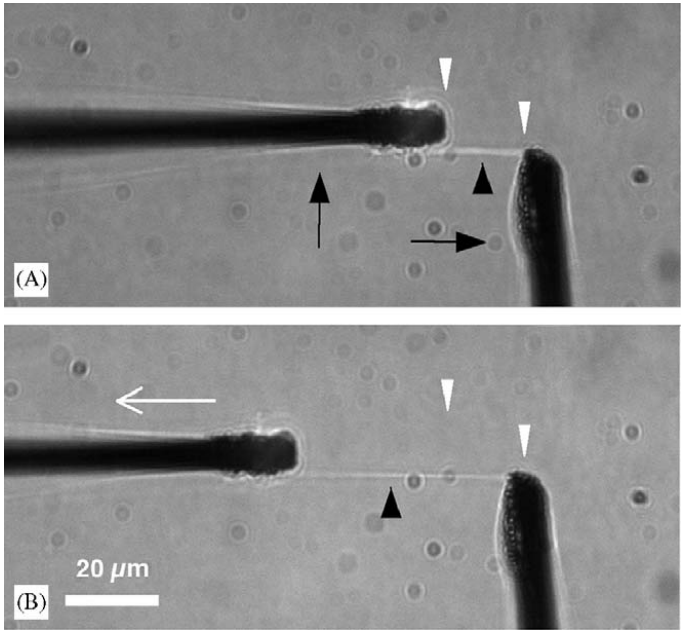


Arterial endothelial cells

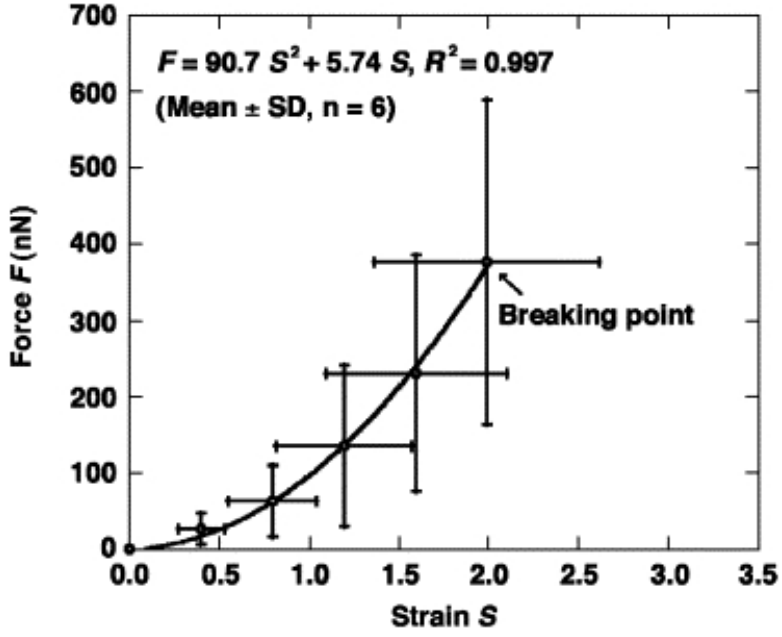
Kaunas et al., PNAS (2005)

Elastic modulus of a stress fiber

Pulling on a stress fiber



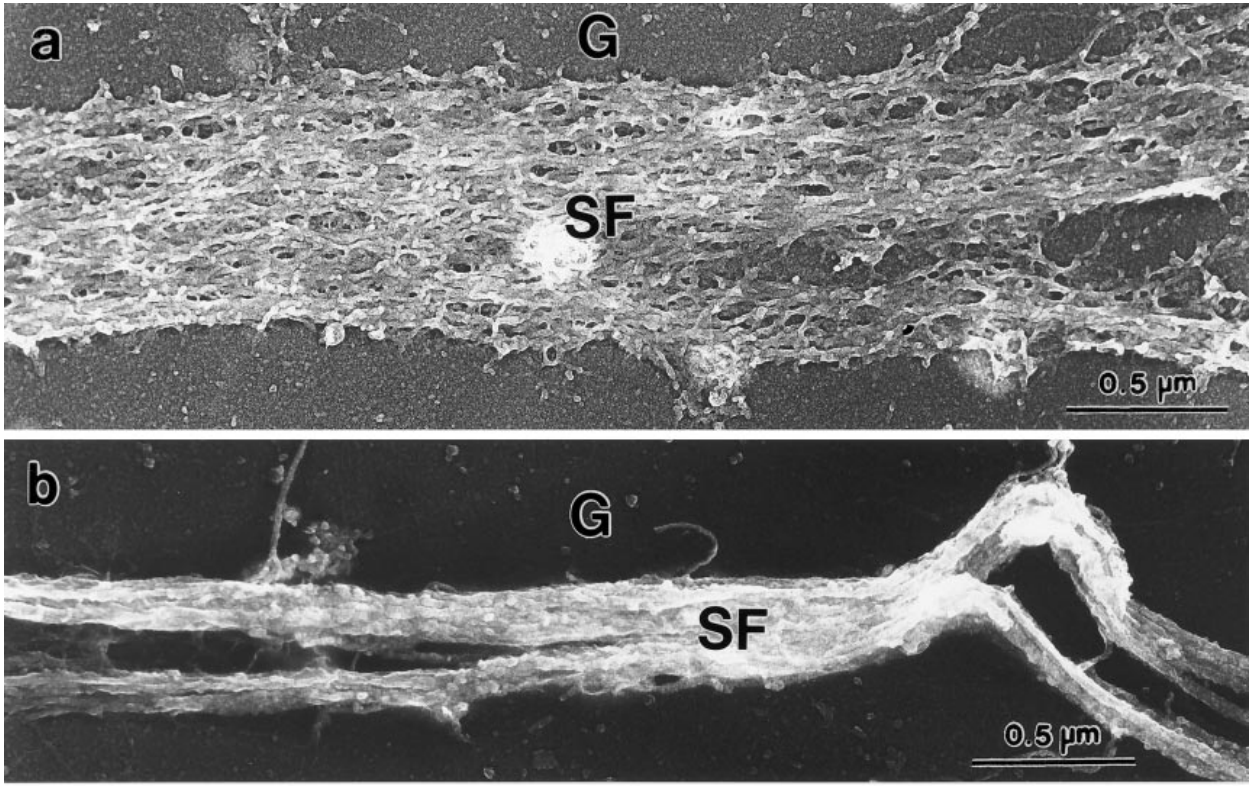
Force-extension data



- Aortic endothelial cells without ATP
- (Linear) elastic modulus $E \approx 10^5 - 10^6$ Pa

Deguchi et al., J. Biomech. (2006)

Stress fibers: active contractility



Stress fibers (a) contract upon addition of ATP (b)

Katoh et al., Mol. Biol. Cell (1998)

General framework: hydrodynamics

Models simple enough to allow for analytical treatment without neglecting crucial physical ingredients.

- ignore signaling
- mesoscopic scales: $\Delta x \gg \xi$ mesh size of the polymer network
- few parameters (elastic moduli,...)

Simplified rheology: constitutive equation for an active solid

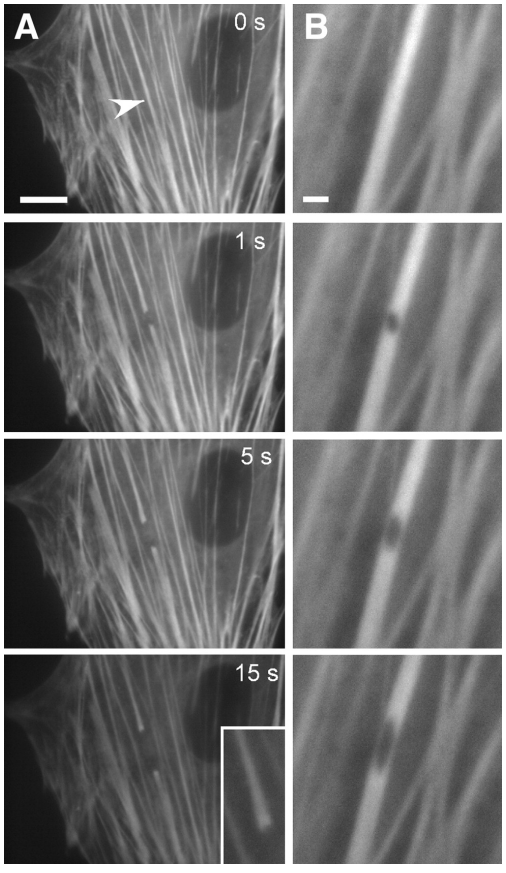
In the simplest case (*e.g.* 1D or isotropic)

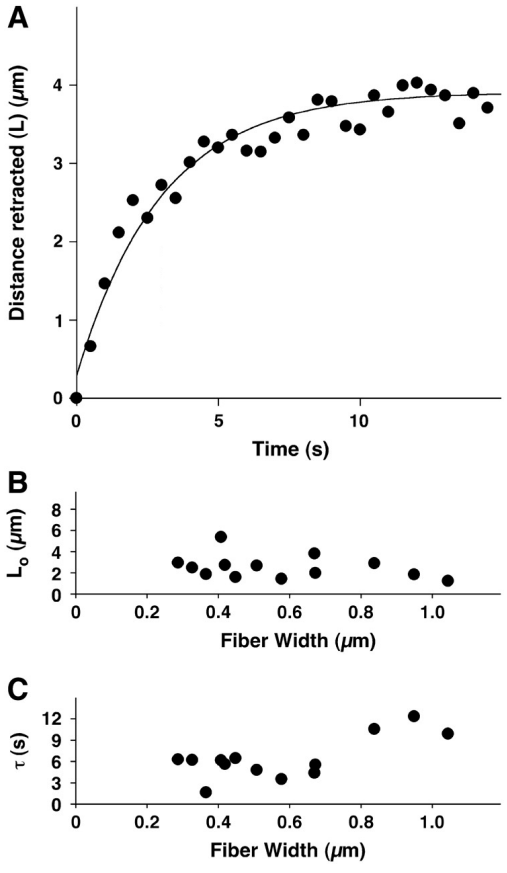
$$\sigma^{\text{total}} = \sigma^{\text{elastic}} + \sigma^{\text{active}} = G\,e + \sigma_A$$

σ: stress; e: strain; G: elastic modulus; σ_A: active stress

Yoshinaga and Marcq, Phys. Biol. (2012)

Ablation of a stress fiber





- Endothelial cells (bar: 2 μm)
- Retracted length: independent of initial radius
- Contraction time: independent of initial radius, seconds

Kumar et al., Biophys. J. (2006)

Physical origin of the retraction time?

Exponential relaxation with a single time scale

$$l(t) = l_0 - \Delta l \left(1 - e^{-t/\tau}\right)$$

Model of the bundle as a viscoelastic solid

$$\tau = \frac{\eta}{E}$$

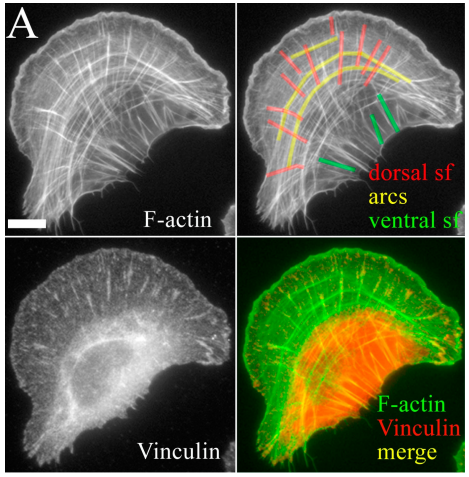
Dissipation due to protein friction

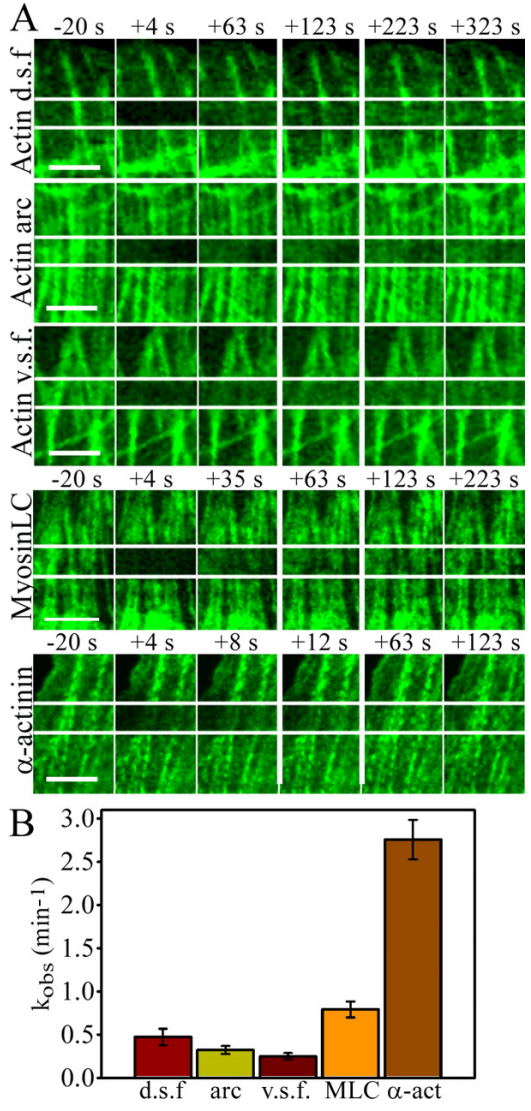
Cross-linker turn-over: strained cross-linkers store elastic energy that is dissipated upon unbinding.

Dynamic proteins

FRAP experiments

Fluorescence Recovery After Photobleaching





- Osteosarcoma cells
- Bar: 5 μm
- Half-recovery time

Hotulainen et al., J. Cell Biol. (2006)

Protein friction explains the viscosity of the bundle

In 1D: $F_z = n_X \, k_X \, v_z \tau_X = \zeta_p \, v_z$

- n_X average number of attached crosslinkers per filament
- k_X spring constant of a crosslinker
- τ_X average binding time of a crosslinker

$$\Rightarrow \zeta_p \approx n_X \, k_X \, \tau_X$$

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In 3D: $\sigma_{zz}^{(p)} = \eta_p\, \frac{\partial v_z}{\partial z} \approx \eta_p\, \frac{U}{L}$, $\sigma_{zz}^{(p)} = n_F \frac{\zeta_p\, v_z}{A}$ and $v_z \approx U\, \frac{l_F}{L}$

- n_F average number of filaments per cross-section
- l_F length of a filament:
- A bundle cross-section

$$\Rightarrow \eta_p \approx n_F\, \frac{l_F}{A}\, \zeta_p$$

Contraction time

Viscosity coefficient $\eta_p \approx n_F n_X \frac{l_F}{A} k_X \tau_X$.

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Elastic modulus $E \approx n_F n_X \frac{l_X}{A} k_X$

Since $\sigma_{zz}^{(el)} = E \frac{\partial u_z}{\partial z} \approx E \frac{\Delta Z}{L}$, $\sigma_{zz}^{(el)} = n_X \frac{k_X \Delta z}{A}$ and $\Delta z \approx \Delta Z \frac{l_X}{L}$

- l_X length of a cross-linker

Contraction time

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- l_X length of a cross-linker

Viscoelastic time $\tau = \frac{\eta_p}{E}$

- $l_F \approx 1\ \mu$m
- $l_X \approx 0.1\ \mu$m
- $\tau_X \approx 1 - 10$ s

$$\Rightarrow \tau \approx \frac{l_F}{l_X} \tau_X \approx 10^1 - 10^2 \text{ s}$$

independent of initial radius and length

Force balance $\eta_p \frac{\mathrm{d}e}{\mathrm{d}t} + E\, e + \sigma_A = 0$

- $l(t)$ bundle length
- $e(t) = \frac{l(t)-l_0}{l_0}$ longitudinal strain
- σ_A active stress

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Strain relaxation $e(t) = e_\infty \left(1 - e^{-t/\tau}\right)$

After relaxation: $e_\infty = -\frac{\sigma_A}{E}$

Initial velocity: $|v_0| = |e_\infty| \frac{l_0}{\tau} \propto \sigma_A$

Active stress

Measurement $\sigma_A = E\,|e_\infty|$ with $|e_\infty| \approx 10^{-1}$

$\Rightarrow\ \sigma_A^{SF} \approx 10^4$ Pa OK!

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Estimate $\sigma_A \approx n_F\, n_X^A\, \frac{F_S}{A}$

- $n_X^A \approx 10$ average number of active crosslinkers per filament
- $F_S \approx 1$ pN stall force of a motor

$\Rightarrow\ \sigma_A^{SF} \approx 10^4$ Pa CONSISTENT

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Retracted length $\Delta l = \frac{\sigma_A}{E}\, l_0 \approx \frac{F_S}{k_X\, l_X}\, l_0$

independent of initial radius

Geometry: cylinder of initial radius a_0 and length L_0

Homogeneous and isotropic material

- elastic moduli (K, G) or (E, ν)
- (bulk) viscosity η_p
- active stress σ_A

Exact solution

When the initial state is the elastic reference state:

$$\frac{L(t) - L_0}{L_0} = \frac{a(t) - a_0}{a_0} = -\frac{\sigma_A}{3K}\left(1 - e^{-t/\tau_K}\right) \quad \text{with } \tau_K = \frac{\eta_p}{3K}$$

The bundle contracts longitudinally and radially independently of the value of the Poisson ratio ν.

Contraction of actomyosin bundles: conclusion

- The contraction time of actomyosin bundles is a viscoelastic time equal to the ratio of protein friction viscosity to elastic modulus
- Simple scaling arguments yieldw
  - $\rightarrow$ the order of magnitude of τ
  - $\rightarrow$ the order of magnitude of σ_A
- Cross-over to visco-poroelasticity when

$$a_0 \gg a_c \approx \left(\frac{n_F \, l_F \, \zeta_p}{\eta_c} \, \xi^2 \right)^{1/4} \approx 10 \; \mu m$$

- Obvious need for more quantitative data, from reconstituted bundles?

Yoshinaga and Marcq, Phys. Biol. (2012)

Outline

Motility of Keratocyte cells

Verkhovsky

Gliding motion

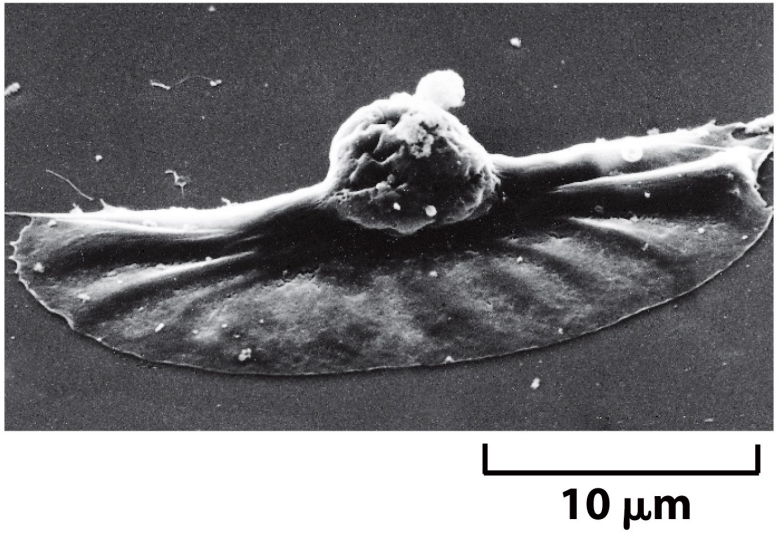


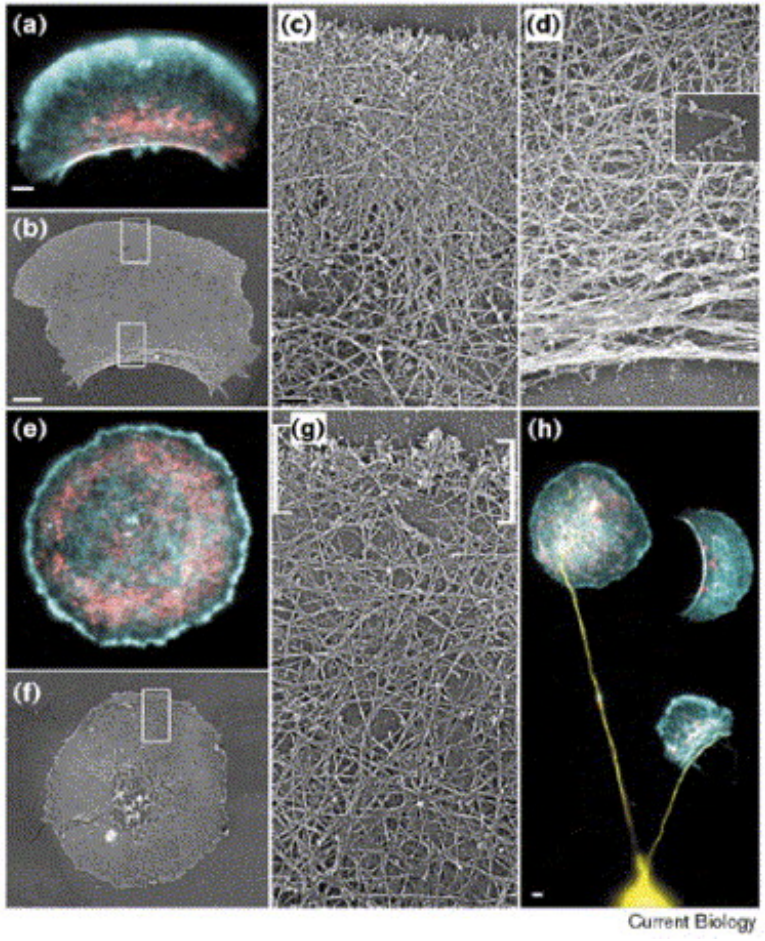
Figure 16-87b Molecular Biology of the Cell 5/e (© Garland Science 2008)

Fish keratocyte

Fast motion: 10μm/min.

Constant shape

Cell fragments



Cell motility: biological model

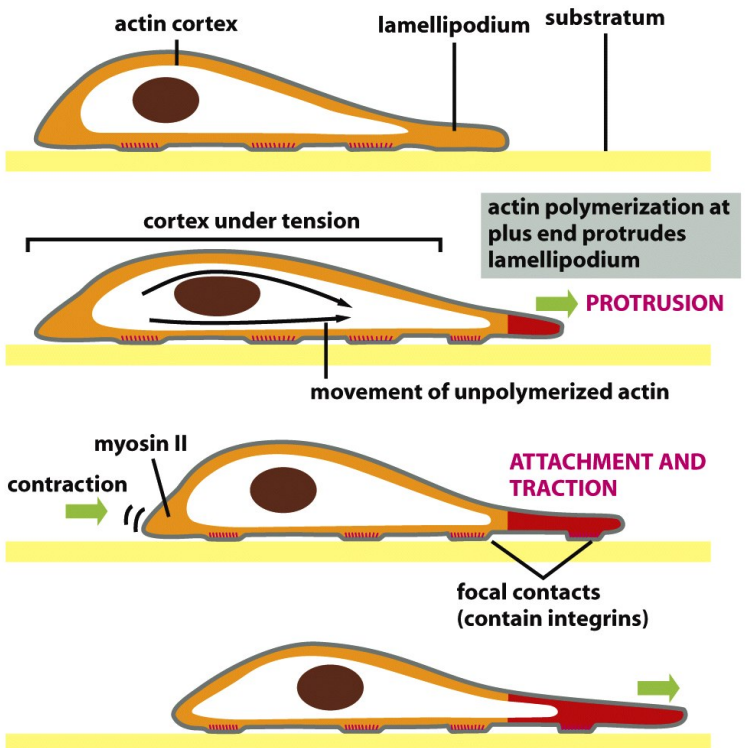
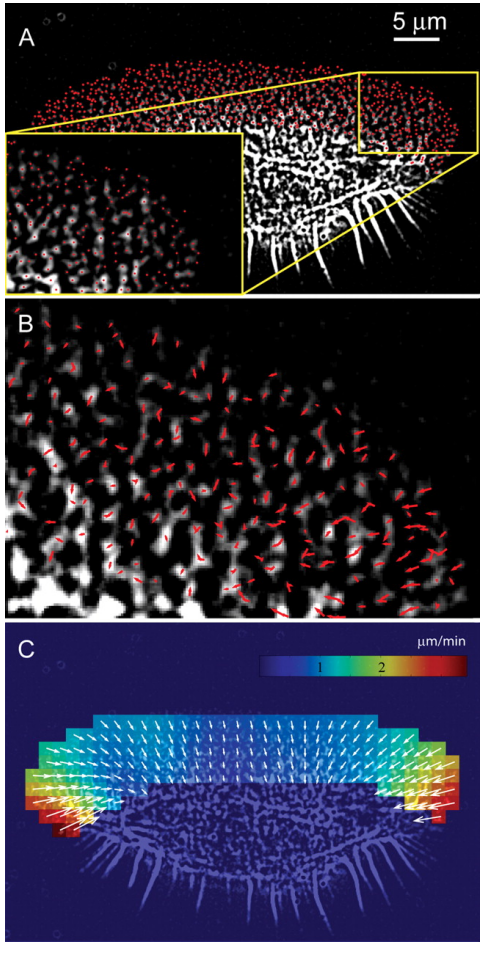


Figure 16-86 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Quantitative data

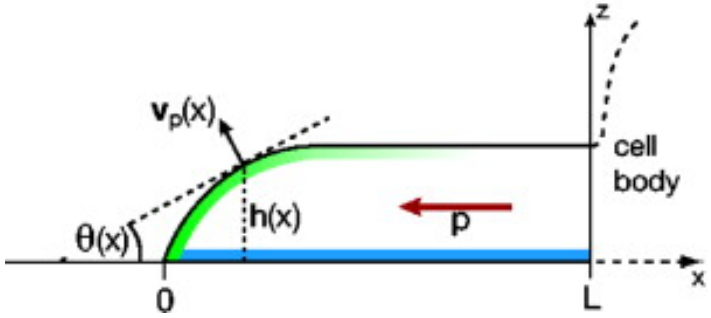
Actin velocity field



Data

- Velocity field obtained by speckle microscopy Valloton et al.
- Advancing velocity $u = 10\,\mu$m/min.
- Retrograde flow $v = 1\,\mu$m/min.
- Stress distribution on the substrate $\sigma_{xz} = 4\ 10^2$ Pa Oliver et al.
- Actin viscosity $\eta = 10^5$ Pa.s Käs et al.

One dimensional lamellipodium



Actin dynamics

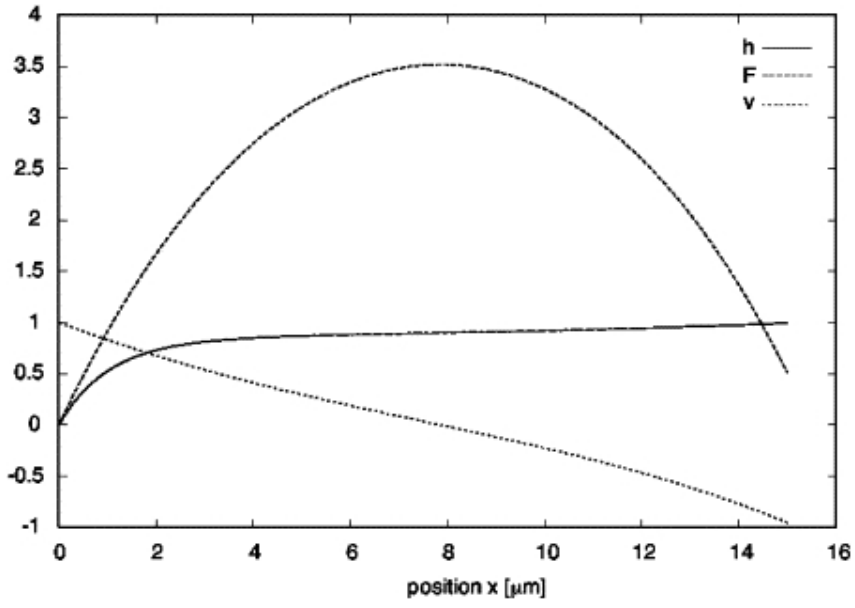
- Fully polarized $p = 1$
- v_p polymerization velocity at the front
- v_d depolymerization velocity at the rear
- $U = v(L) + v_d = v(0) + v_p$

Mechanics

- Mass conservation $\frac{\mathrm{d}}{\mathrm{d}x} h(v + U) = k_p \, \rho_{wa}(x)$
- Active viscous liquid $\sigma = 2\eta \frac{\partial v}{\partial x} + \sigma_A$
- Momentum conservation $\frac{\mathrm{d}}{\mathrm{d}x} h\sigma = \xi v$

Results

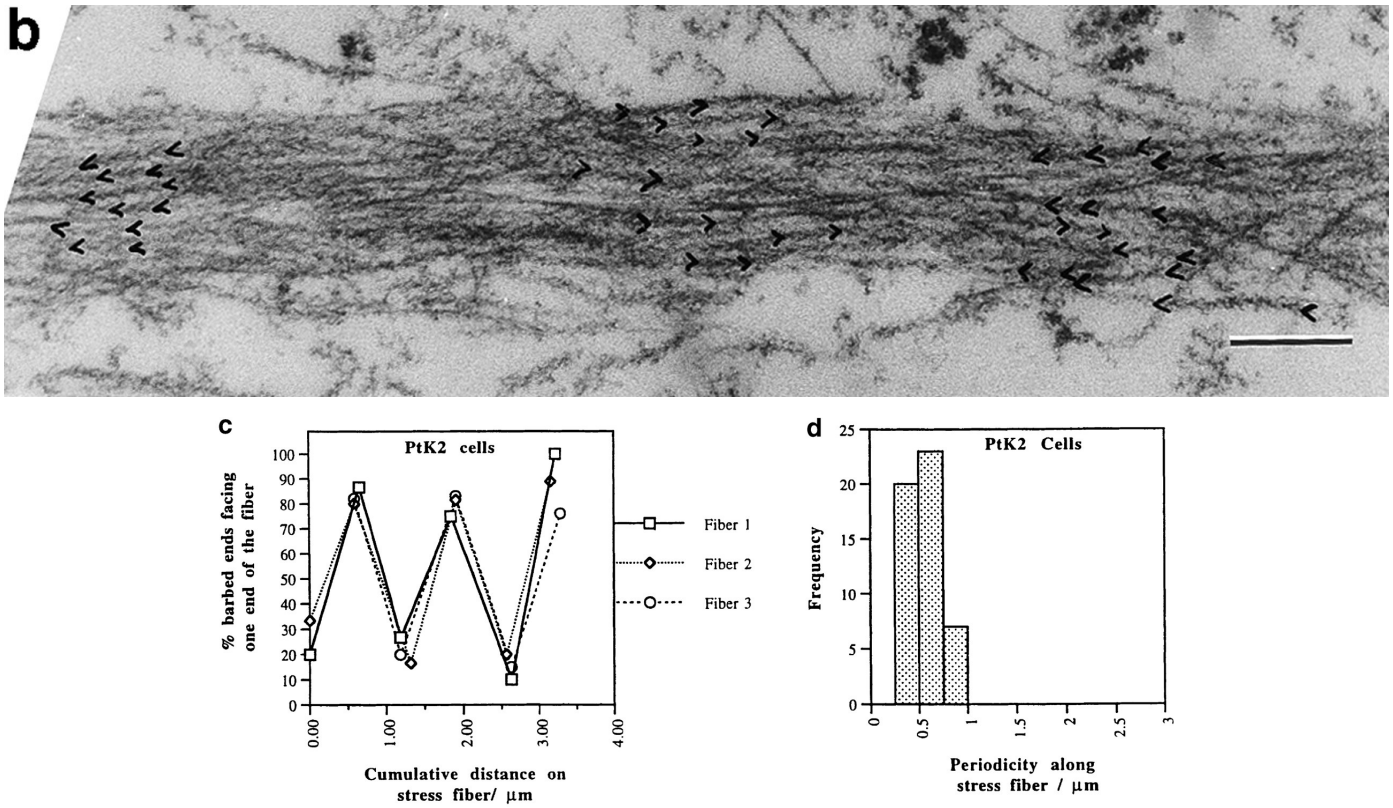
- No movement at the center of lamellipodium
- Retrograde flow at the front
- Anterograde flow at the rear
- Zero total cell-substrate force
- Non-zero external force dipole



Kruse et al. Phys. Biol. 2006

Outline

A polar structure: alternating polarity

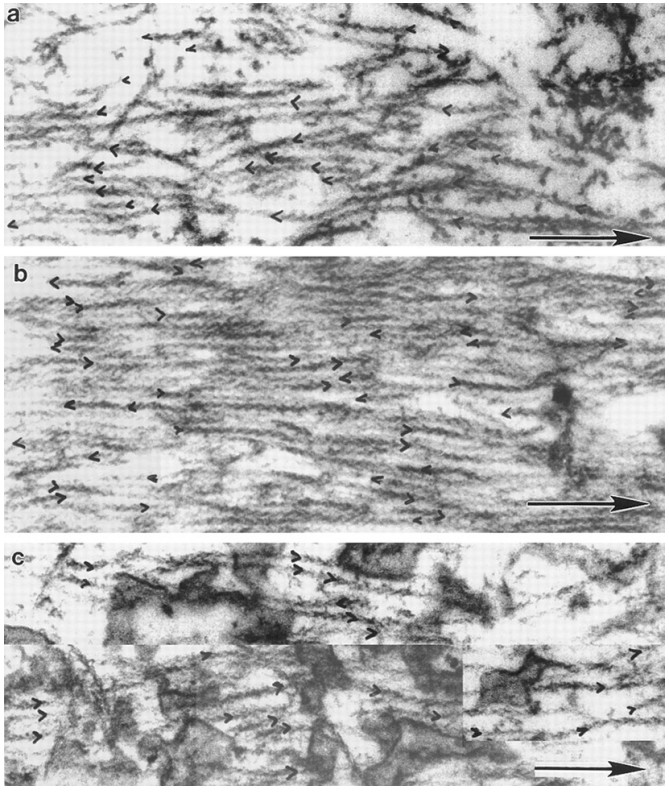


- Ptk2 cells (kidney epithelium), bar: 0.2 μm
- Actin decorated with S1 myosin heads
- Wavelength $\lambda \simeq 1\ \mu$m

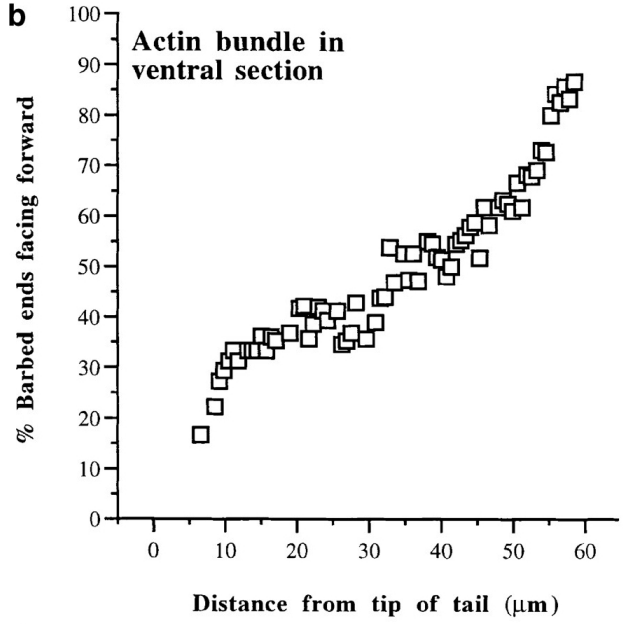
Cramer et al., J. Cell Biol. (1997)

A polar structure: graded polarity

Onset of motility



Fibroblasts bar: 0.2 μm



Cramer et al., J. Cell Biol. (1997)

Stress fiber as a 1D active polar elastomer

Hydrodynamic model of a stress fiber...

- on mesoscopic scales
- in 1D
- as a one-component system
- elasticity: G
- activity: $\Delta\mu$
- polarity: a, K, γ
- coupling between polarity and elasticity: w
- coupling between polarity and activity: α, β

Polar order parameter $\quad \mathbf{p} = p(z,t)\,\mathbf{e_z}$

- Mesoscopic average of the polarity of actin filaments
- Boundary conditions: $p(0,t) = -1 \quad p(L,t) = +1$
  (barbed ends face focal adhesions)

Yoshinaga et al., Phys. Rev. Lett. (2010)

Statics

Invariance under $p \to -p$, $z \to -z$

Free energy density

obtained by quadratic expansion close to $p = 0$, $e = 0$

$$f = \frac{1}{2} a\, p^2 + \frac{1}{2} K \left(\frac{\partial p}{\partial z}\right)^2 + \frac{1}{2} G\, e^2 + w\, e \left(\frac{\partial p}{\partial z}\right)$$

Thermodynamic stability $\Rightarrow w^2 \leq K\, G$

Conjugate variables

$$\begin{aligned} \text{molecular field } h &= -\frac{\delta f}{\delta p} &&= -\, a\, p + K\, \partial_z^2 p + w\, \partial_z e \\ \text{elastic stress } \sigma^{\text{el}} &= \frac{\delta f}{\delta e} &&= G\, e + w\, \partial_z p. \end{aligned}$$

Constitutive relations

Entropy production rate

From thermodynamics and conservation equations:

$$\frac{R}{T} = \left(\sigma + P - \sigma^{\mathrm{el}}\right)\ \partial_z v + h\,\dot{p} + \Delta\mu\ r$$

The 'chemical' term $\Delta\mu\ r$ models motor activity.

Linear couplings between fluxes and forces

$$\begin{aligned} \sigma + P - \sigma^{\mathrm{el}} &= \eta\ \partial_z v + (-\zeta + \beta\ \partial_z p)\ \Delta\mu \\ \dot{p} &= \frac{h}{\gamma} - \alpha\ p\partial_z p\ \Delta\mu \end{aligned}$$

Passive fiber $\Delta\mu = 0$

Force balance

$$\partial_z \sigma = 0 \;\Rightarrow G\,\partial_z e + w\,\partial_z^2 p = 0$$

Polarization dynamics

$$\tau_p \frac{\partial p}{\partial t} = -p + l^2 \frac{\partial^2 p}{\partial z^2}$$

- $\tau_p = \frac{\gamma}{a} > 0$
- $l^2 = \frac{K}{a}\left(1 - \frac{w^2}{GK}\right) > 0$

Stationary solution: monotonically increasing polarity

$$p(z) = -\cosh(z/l) + \frac{1 + \cosh(L/l)}{\sinh(L/l)} \sinh(z/l)$$

Without contractility: polarity patterns are graded

Active fiber $\Delta\mu \neq 0$

Force balance

$$\partial_z \sigma = 0 \;\Rightarrow G\,\partial_z e + (w + \beta\,\Delta\mu)\;\partial_z^2 p = 0$$

Polarization dynamics damped Burgers equation

$$\frac{\partial p}{\partial t} + \alpha\Delta\mu\, p\,\frac{\partial p}{\partial z} = -\frac{a}{\gamma}\,p + D\,\frac{\partial^2 p}{\partial z^2}$$

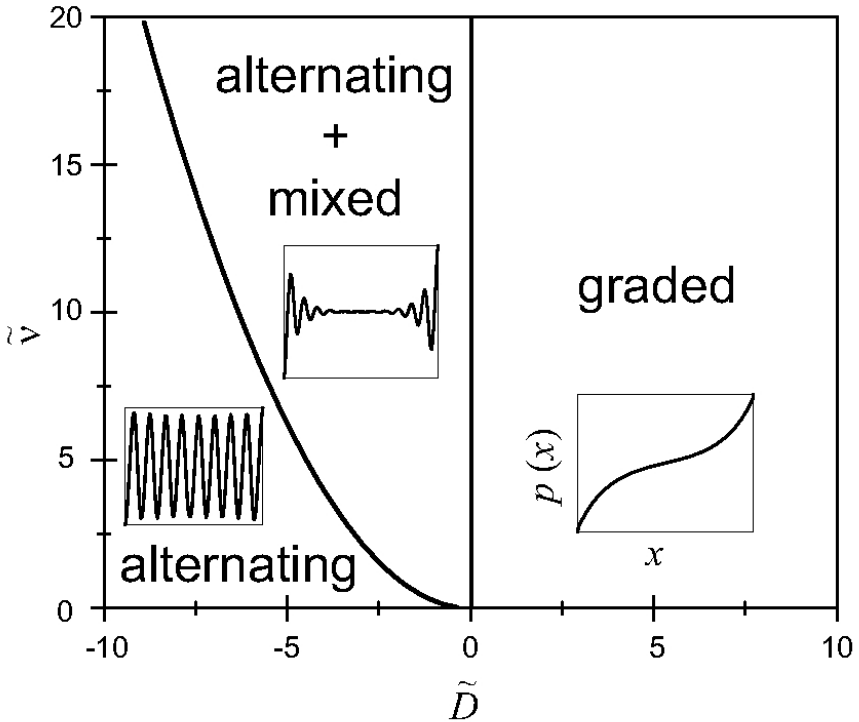
$$D = \frac{K}{\gamma}\left[1 - \frac{w^2}{KG}\left(1 + \frac{\beta\Delta\mu}{w}\right)\right]$$

Diffusion constant may change sign

$D = 0$ when $\frac{\beta\Delta\mu}{w} = \frac{KG}{w^2} - 1$

Active fiber $\Delta\mu \neq 0$

Phase diagram

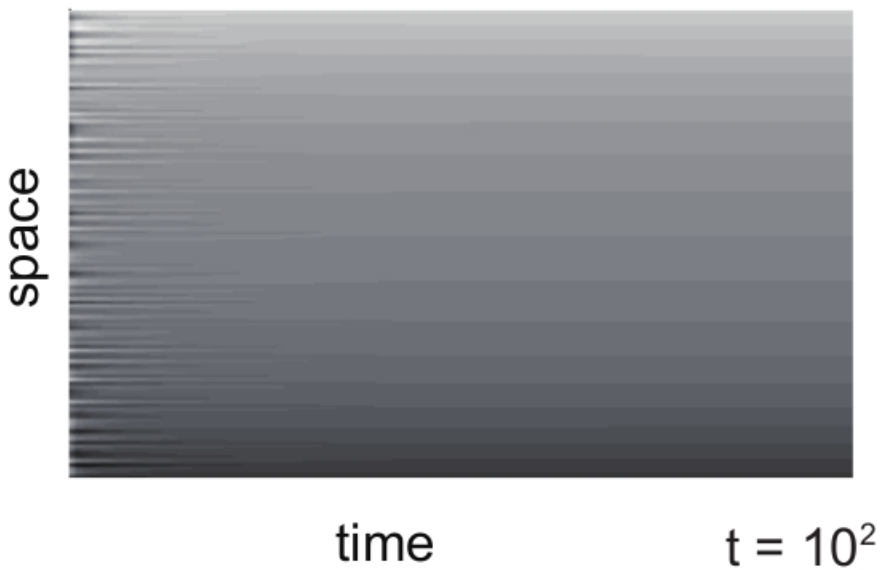


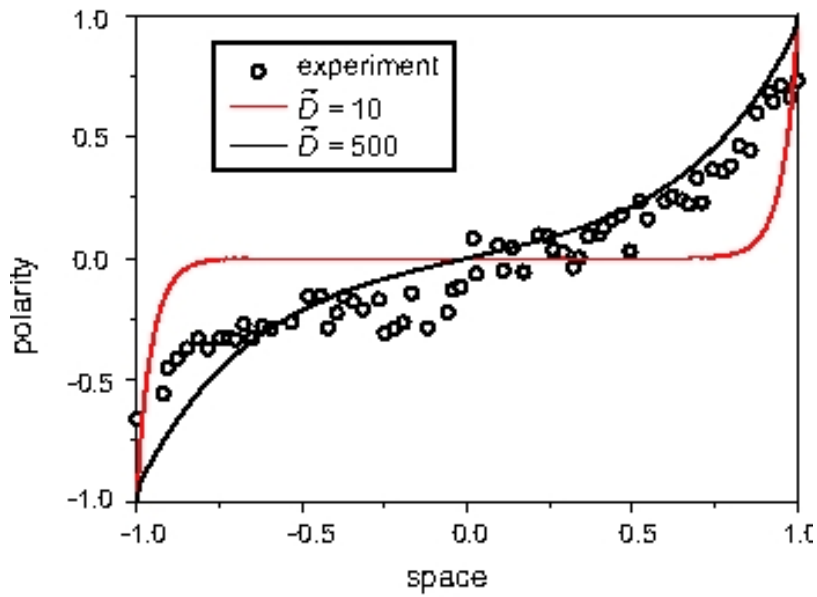
$D > 0$: graded polarity pattern

$$\frac{\beta \Delta \mu}{w} < \frac{KG}{w^2} - 1$$

Evolution equation for the polarity field

$$\frac{\partial p}{\partial \tilde{t}} + p \frac{\partial p}{\partial \tilde{z}} = -p + \tilde{D} \frac{\partial^2 p}{\partial \tilde{z}^2}$$





$\tilde{D} < \tilde{D}_c = -2\sqrt{\tilde{\nu}} < 0$: alternating polarity pattern

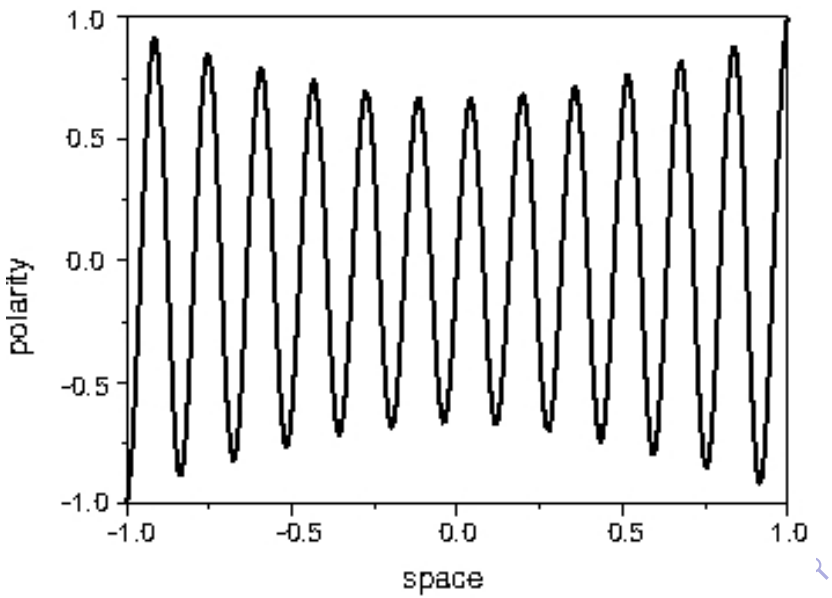
Evolution equation for the polarity field

$$\frac{\partial p}{\partial \tilde{t}} + p\frac{\partial p}{\partial \tilde{z}} = -p + \tilde{D}\,\frac{\partial^2 p}{\partial \tilde{z}^2} - \tilde{\nu}\frac{\partial^4 p}{\partial \tilde{z}^4}$$

Existence of stable periodic stationary solutions with a wavelength λ:

$$\lambda^2 = \frac{8\pi^2\nu}{K}\left[\frac{w^2}{KG}\left(1+\frac{\beta\Delta\mu}{w}\right) - 1\right]^{-1}$$

t = 10^4



Polarity patterns: conclusions

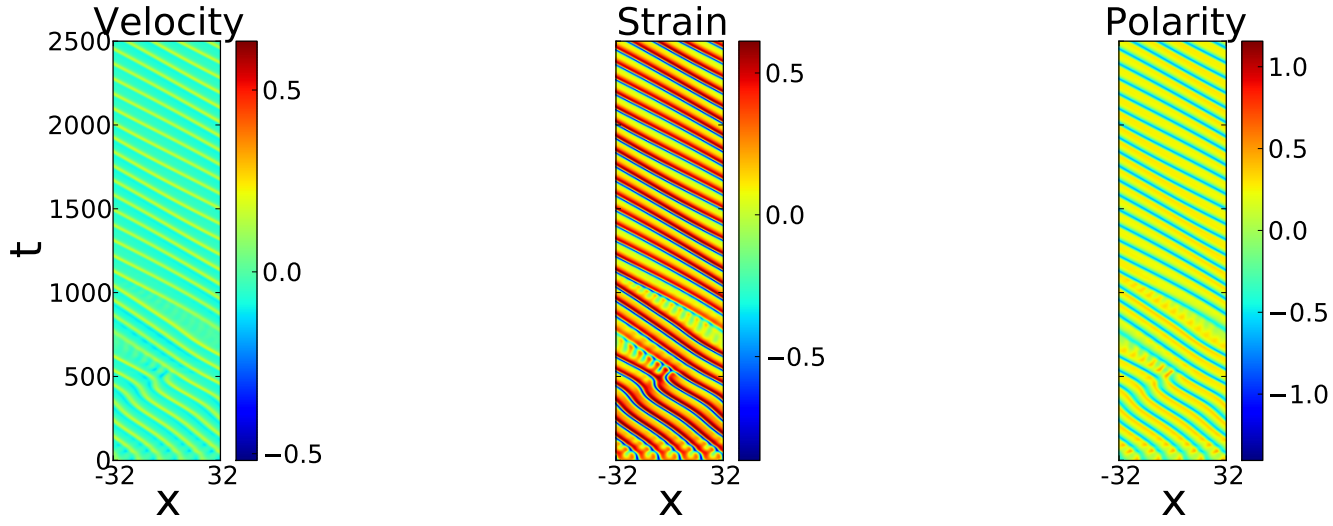
- A bifurcation explains the existence of graded and alternating polarity patterns in stress fibers.
- Active contractility is a necessary condition for the emergence of alternating polarity patterns.
- The wavelength of alternating polarity patterns is a function of the contractility and of the stiffness of the fiber.

$$\lambda^{-2} = a + b\ \Delta\mu$$
$$\lambda^{-2} = c + d/G$$

- The bifurcation also occurs for viscoelastic materials.

Secondary bifurcation: propagating waves

Rheology: (Maxwell) viscoelastic liquid



Here with periodic boundary conditions: rotating ring

Possible applications

- Rotating contractile ring during cytokinesis
- Mechanical waves in collectively migrating epithelia

Marcq, Eur. Phys. J. E (2014)

Acknowledgements

Physico-Chimie Curie

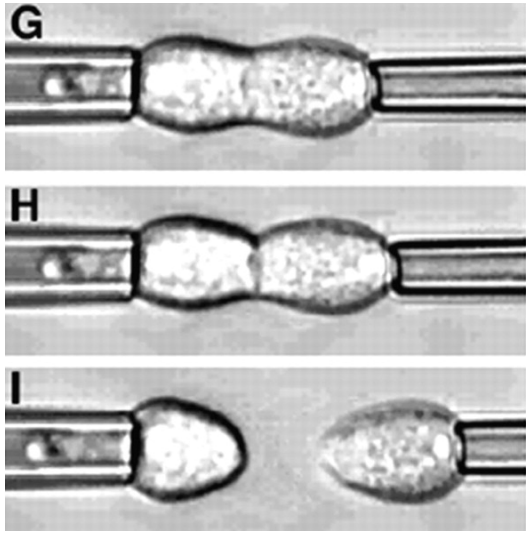
- Jean-François Joanny
- Jacques Prost

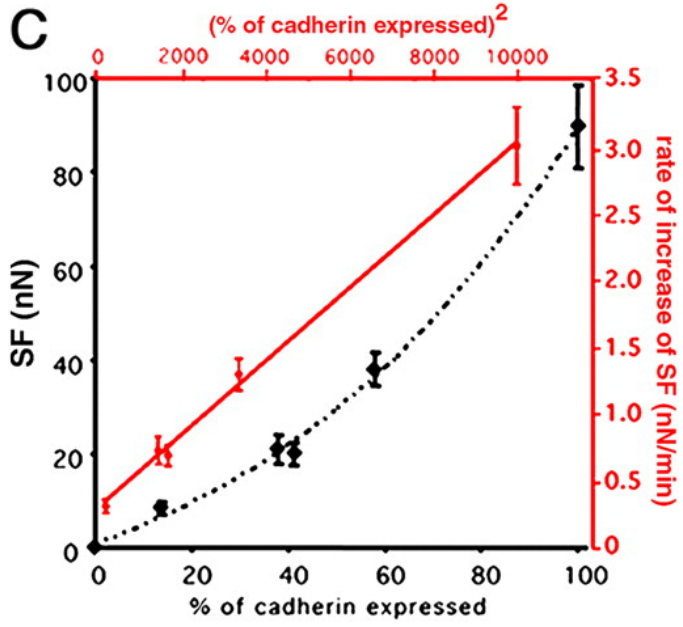
Tohoku University

- Natsuhiko Yoshinaga

Cadherin-mediated cell-cell adhesion

Measurement of cell-doublet separation force





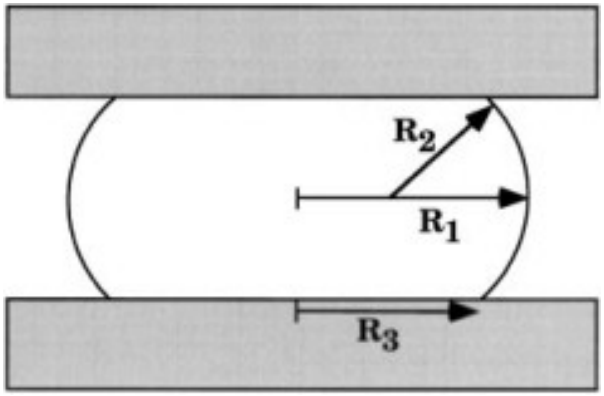
Murine sarcoma S180 cells with variable E-Cadherin expression

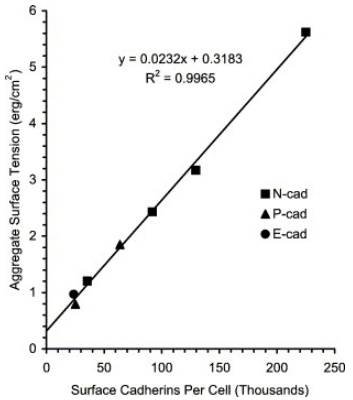
Chu et al. J. Cell Biol. 2004

Outline

Surface tension of a cellular aggregate

Measurement $\sigma = \frac{F}{2\pi R_3^2}\left(\frac{1}{R_1}+\frac{1}{R_2}\right)^{-1} \approx 1-10\,\mathrm{mN\,m^{-1}}$





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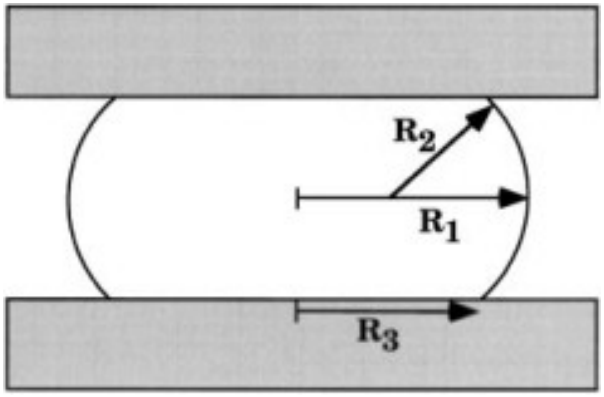
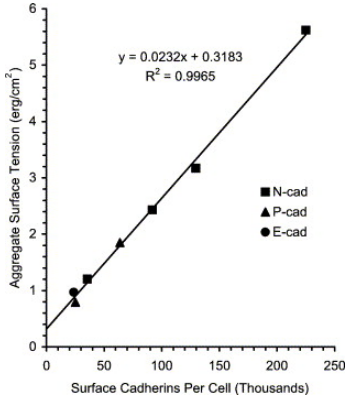
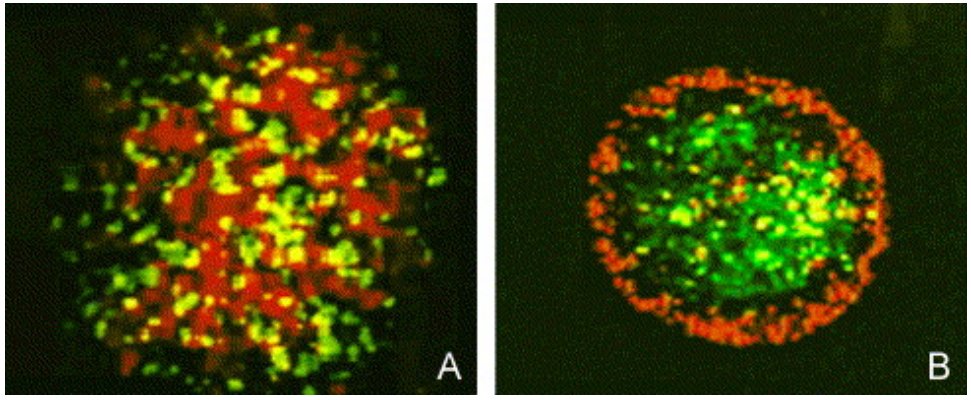


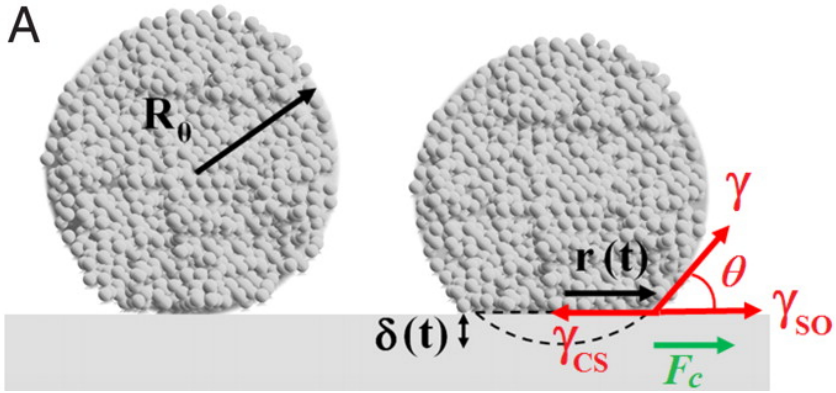


Cell sorting



Foty et al. Dev. Biol. 2005

Spreading of a cellular aggregate (I)



Spreading coefficient $S = \gamma_{SO} - (\gamma_{CS} + \gamma)$

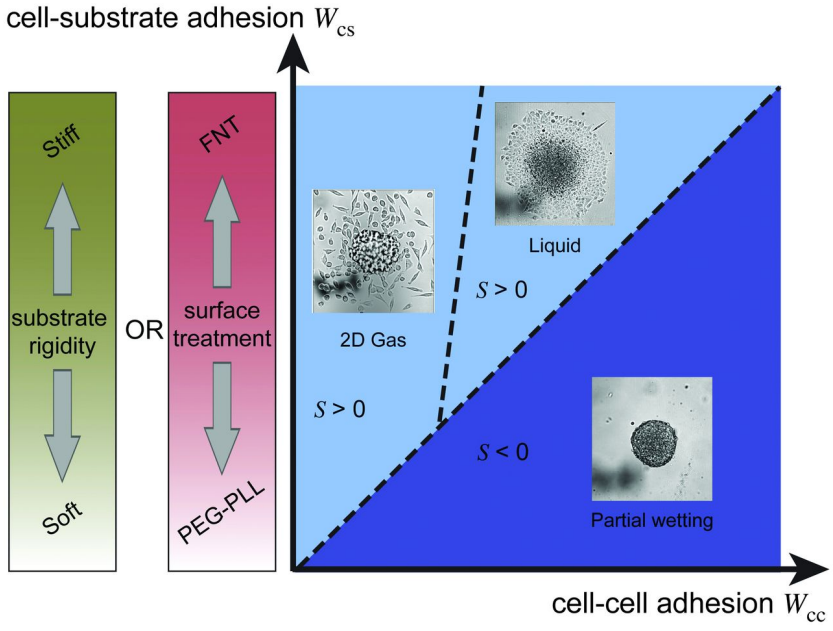
Since $\gamma_{CS} = (\gamma_{SO} + \gamma) - W_{CS}$ and $2\gamma = W_{CC}$, we also have

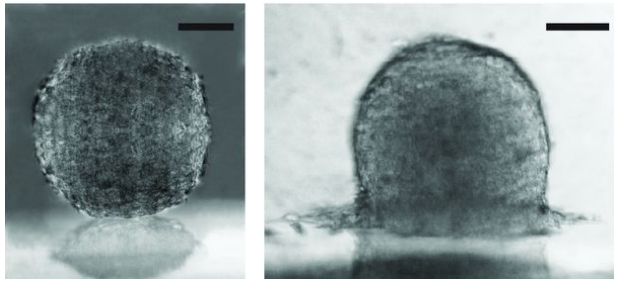
$$S = W_{CS} - W_{CC}$$

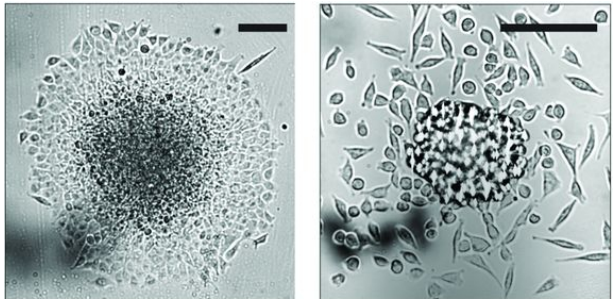
- if $S < 0$, θ is finite: partial wetting
- if $S > 0$, the drop spreads: complete wetting

Douezan et al. PNAS 2011

Spreading of a cellular aggregate (II)



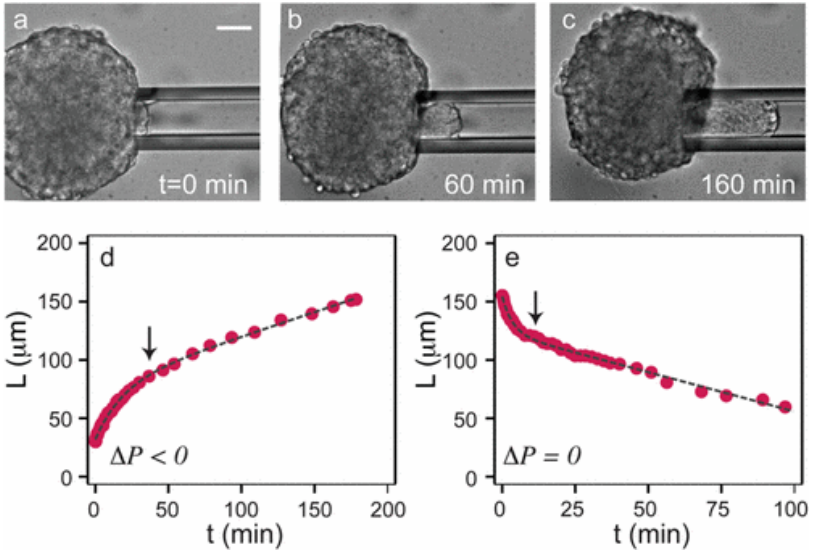




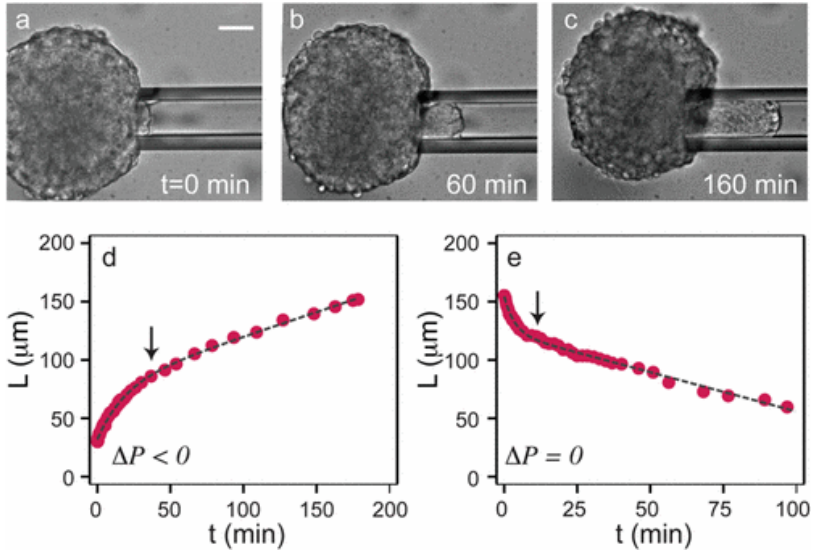
In vitro Epithelial-Mesenchymal Transition?

Gonzalez-Rodriguez et al. Science 2014

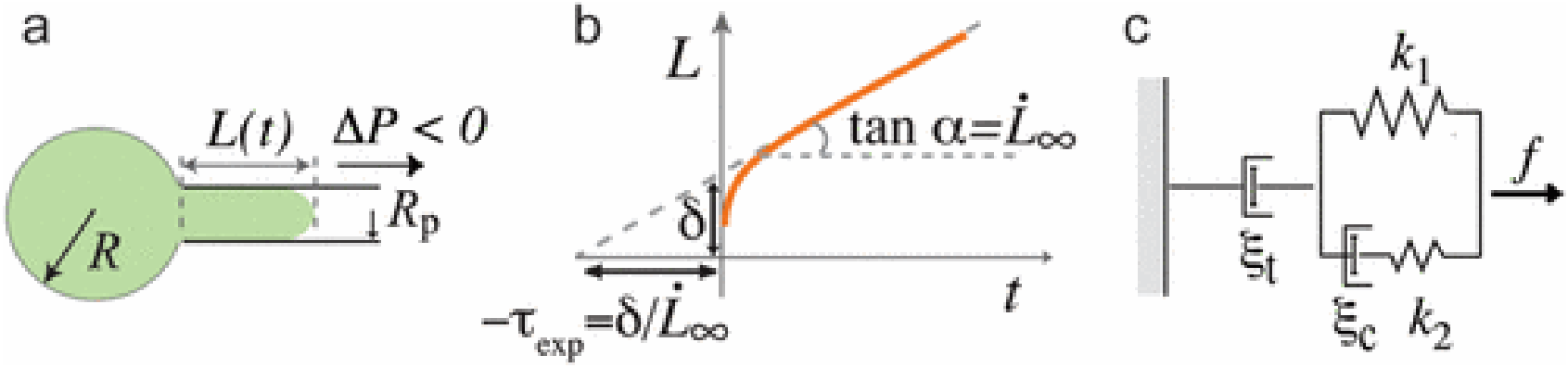
Aspiration of a cellular aggregate (I)



Aspiration of a cellular aggregate (I)



A viscoelastic liquid $L(t) = \frac{f}{k_1}\left(1 - \frac{k_2}{k_1+k_2}\, e^{-t/\tau_c}\right) + \frac{f}{\xi_t}\, t$



Guevorkian et al. Phys. Rev. Lett. 2010

Aspiration of a cellular aggregate (II)

Orders of magnitude

- Elastic modulus $E \approx 700$ Pa
- Viscosity $\eta \approx 2\,10^5$ Pa s
- Surface tension $\gamma \approx 5$ mN m^{-1}

Aspiration of a cellular aggregate (II)

Orders of magnitude

- Elastic modulus $E \approx 700$ Pa
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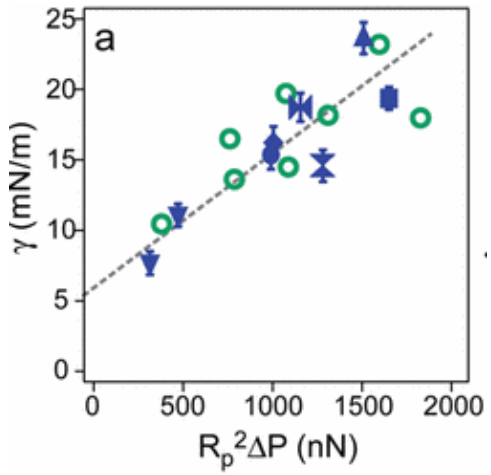
- Surface tension $\gamma \approx 5$ mN m^{-1}

Active reinforcement of the surface tension $\Delta P_c = 2\gamma(\frac{1}{R_p} - \frac{1}{R})$

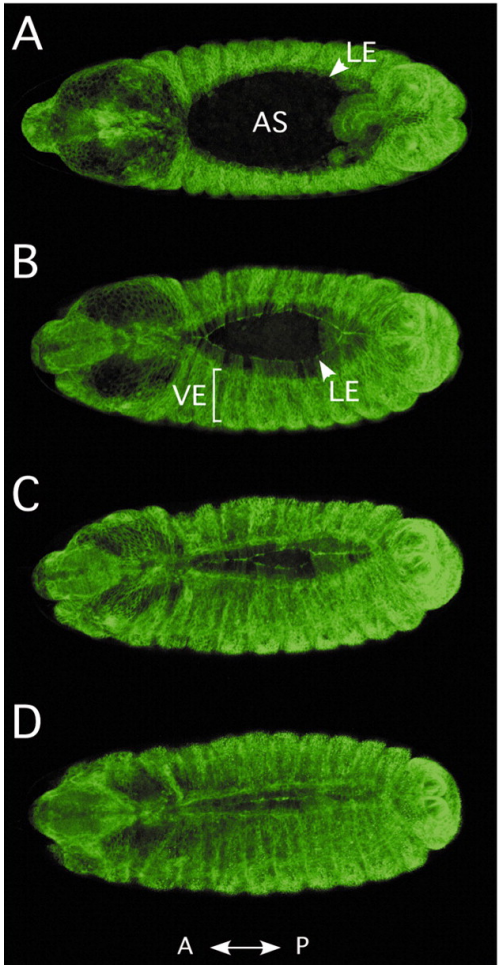


Guevorkian et al. Phys. Rev. Lett. 2010

Outline

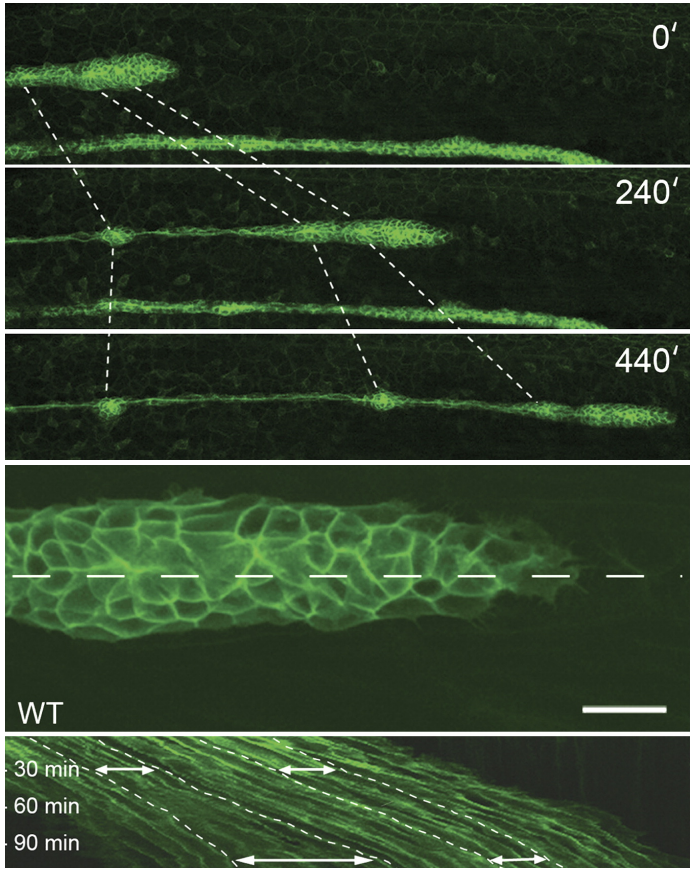
Motivation: collective cell migration during development

Drosophila dorsal closure



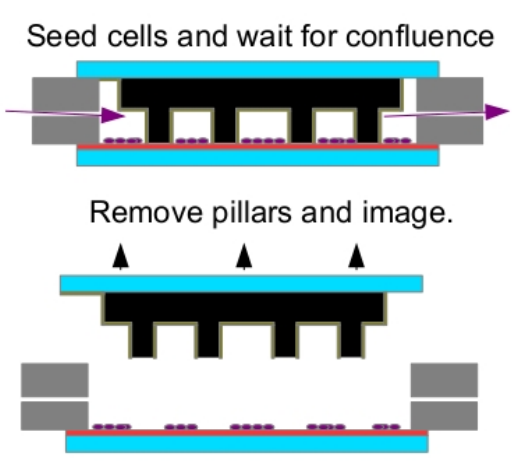
Martin et al. Dev. 2004

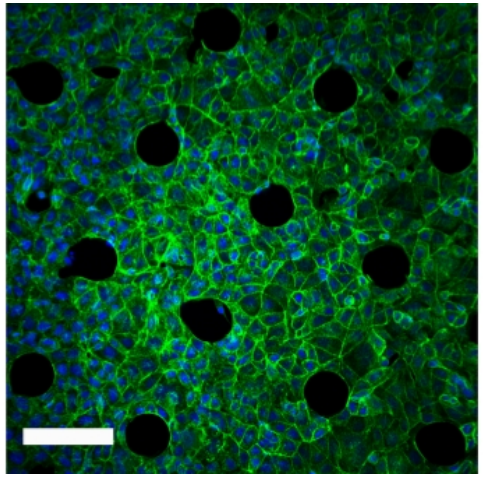
Zebrafish
Lateral line primordium



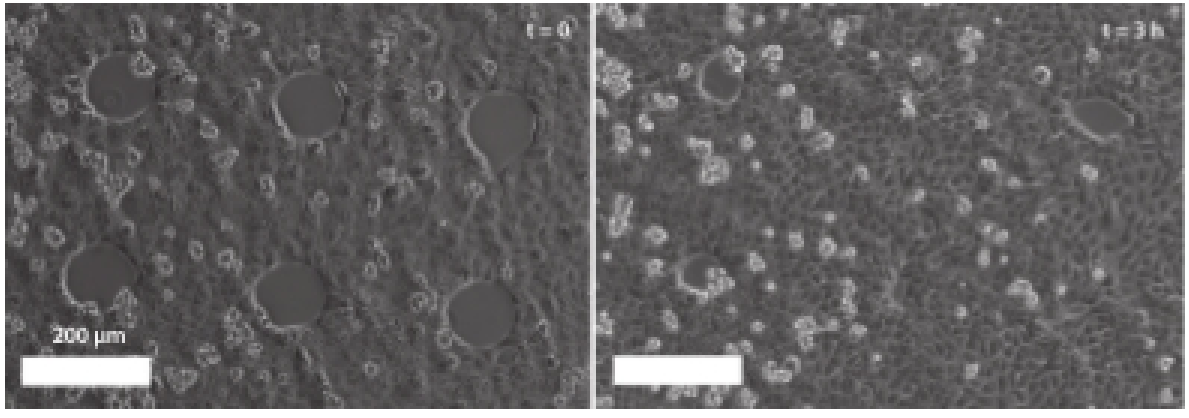
Haas et al. Dev. Cell 2006

Model wounds: experimental set-up





Example of an experiment, GFP-actin



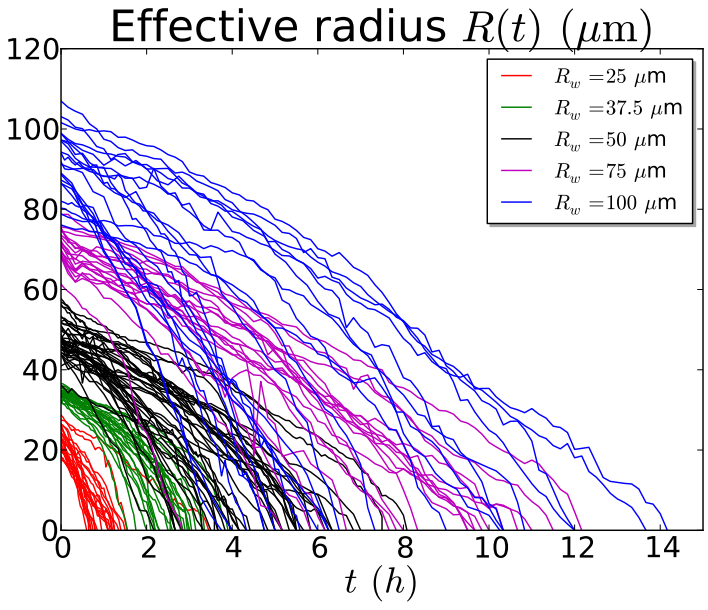
Large variability

Cochet-Escartin et al., Biophys. J. (2014)

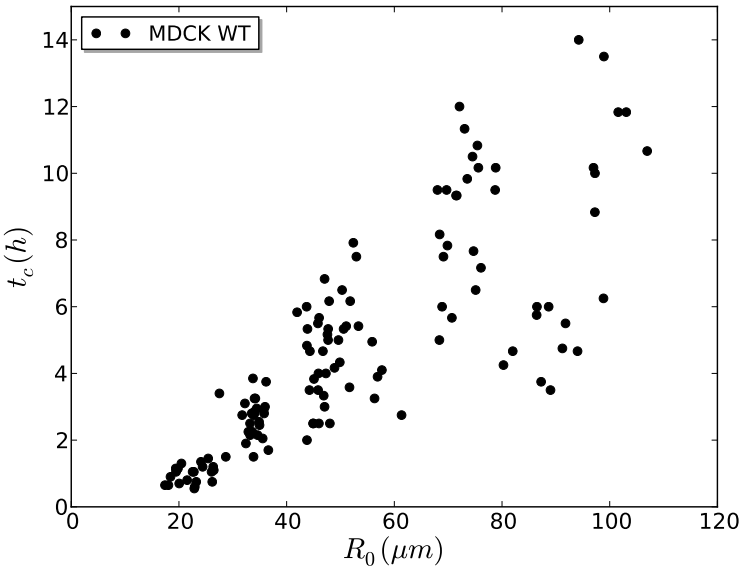
Quantitative data

MDCK cells

Trajectories



Closure time



Model

No apoptoses and few cell divisions ($t_{\text{div}} \approx 20\,\text{h}$)
Few cell rearrangements
Homogeneous, isotropic material

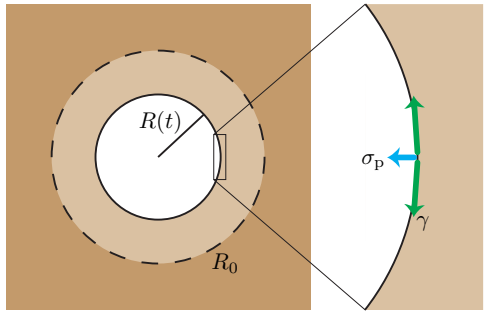
Incompressibility: $\operatorname{div} \vec{v} = 0 \Rightarrow v_r(r,t) = \dfrac{R(t)\dot{R}(t)}{r}$

Force balance $\qquad \operatorname{div} \sigma = \xi \vec{v}$

Constitutive equation $\qquad \sigma_{rr} = -p(r,t)$

Boundary conditions $\qquad \sigma_{rr}(r = R(t)) = \sigma_p$

$\sigma_{rr}(r = R_{\text{max}}) = -p_0$

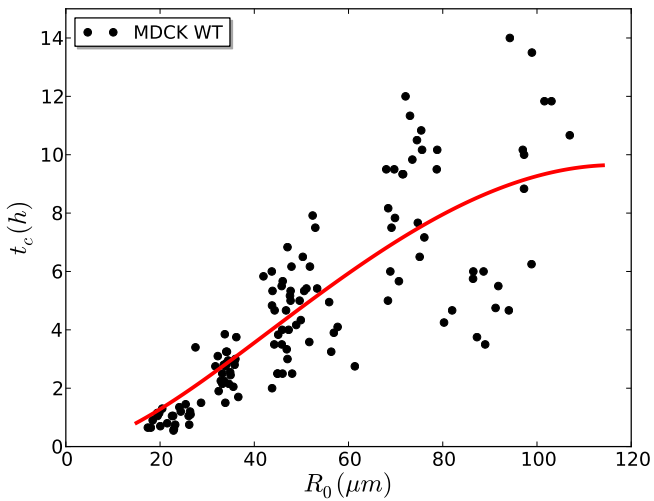


Simplest model: inviscid fluid, no cable

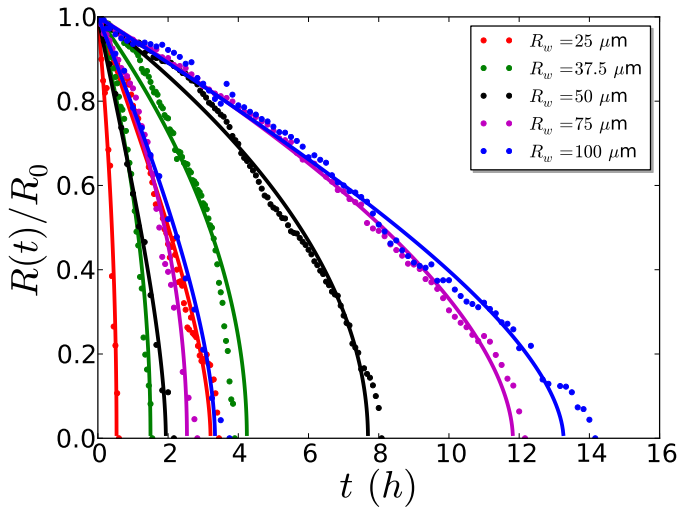
Epithelization coefficient $D = \frac{\sigma_p}{\xi}$

Cut-off radius $R_{\max}$

Closure time



Trajectories



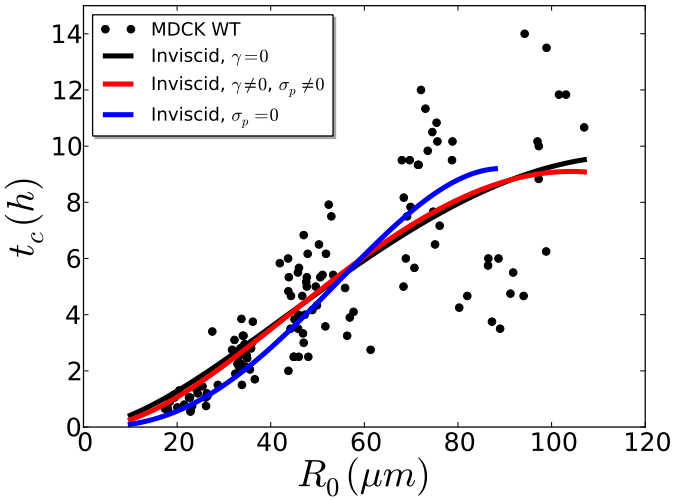
$D = 353 \pm 38\,\mu\mathrm{m}^2\,\mathrm{h}^{-1}$

$R_{\max} = 117 \pm 11\,\mu\mathrm{m}$

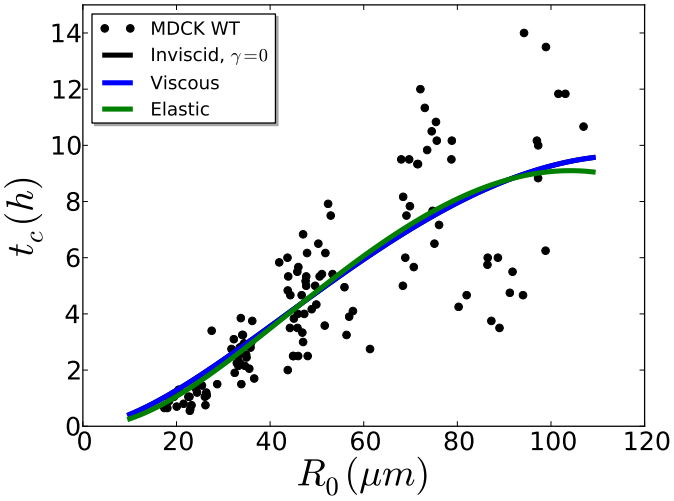
$$t(R) = \frac{R_0^2}{4D}\left(1 + 2\ln\left(\frac{R_{\max}}{R_0}\right)\right) - \frac{R^2}{4D}\left(1 + 2\ln\left(\frac{R_{\max}}{R}\right)\right),$$

Alternative hypotheses

Border forces



Tissue rheology



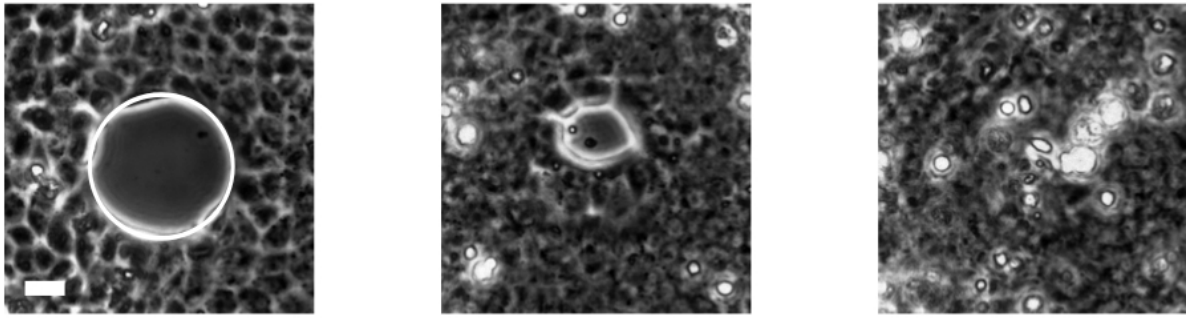
The following additional ingredients are negligible:

- Cable tension: $\frac{\gamma}{\sigma_p R_0} \ll 1$
- Epithelial viscosity: $\frac{\eta}{\xi R_0^2} \ll 1$
- Epithelial elasticity: $\frac{\mu}{\sigma_p} \ll 1$

Conclusions

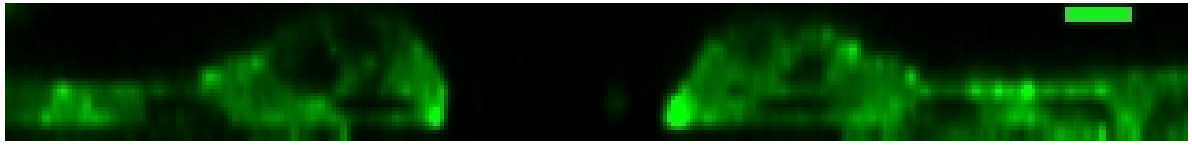
- protrusive stress σ_p dominates force generation
- epithelium-substrate friction ξ dominates dissipation
- closure dynamics is characterized by the epithelization coefficient $D = \sigma_\mathrm{p}/\xi$
- measured values of D allow to tell apart cell types and conditions
- order of magnitude estimate of the friction coefficient $\sigma_p/\xi \approx 10^2\,\mu\mathrm{m}^2\,\mathrm{h}^{-1}$ and $F_p \approx 1\ \mathrm{nN} \quad \Rightarrow \xi \approx 1\,\mathrm{nN}\,\mu\mathrm{m}^{-3}\,\mathrm{s}$

Closure dynamics on a non-adhesive substrate



0 h 30 h 60 h

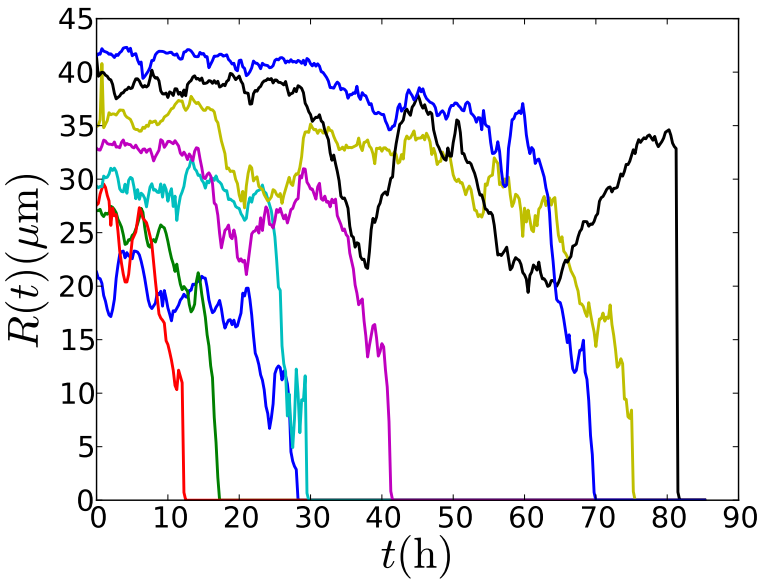
- Without protrusions
- Without friction
- Longer closure time $t_c \simeq 10\,\mathrm{h}$
- With a contractile pluricellular cable



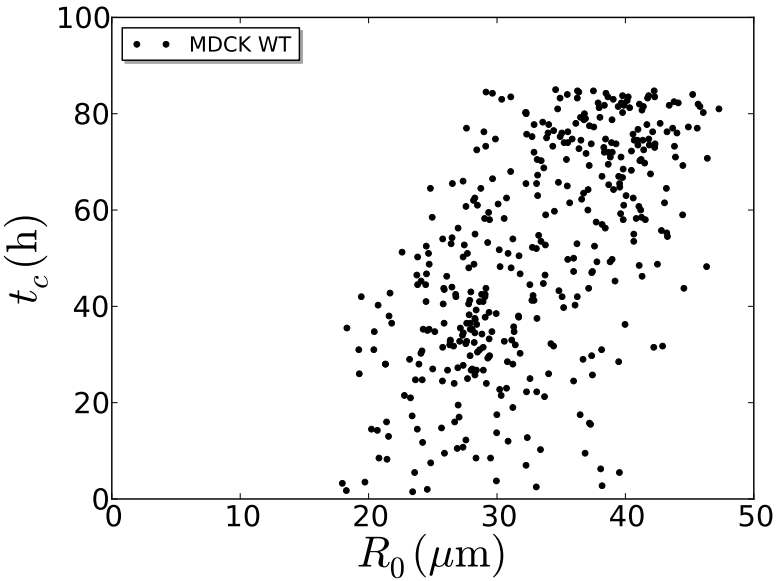
Maxime Deforet, Guillaume Duclos

Experimental data: noisy wound healing

Trajectories



Closure times



Model

Force balance at the tissue edge

$$-\zeta \dot{r} - \frac{\gamma}{r} + F(t) = 0$$

- ζ effective friction coefficient
- γ line tension of the contractile cable
- $F(t)$ random force

Model

Force balance at the tissue edge

$$-\zeta \dot{r} - \frac{\gamma}{r} + F(t) = 0$$

- ζ effective friction coefficient
- γ line tension of the contractile cable
- $F(t)$ random force

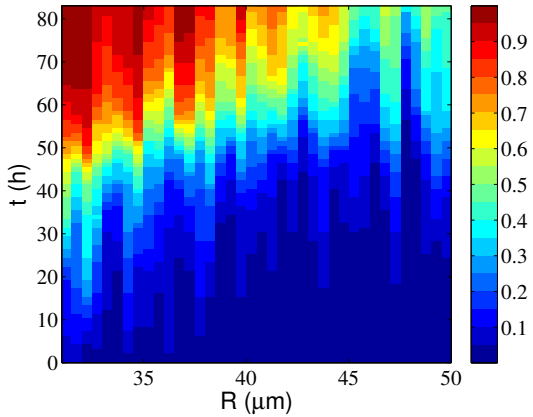
$$\dot{r} = -\frac{\gamma^*}{r} + \sqrt{2D}\,\eta(t)$$

Parameters

- $\gamma^* = \frac{\gamma}{\zeta}$ reduced line tension
- D diffusion coefficient
- η Gaussian white noise

Probabilistic description

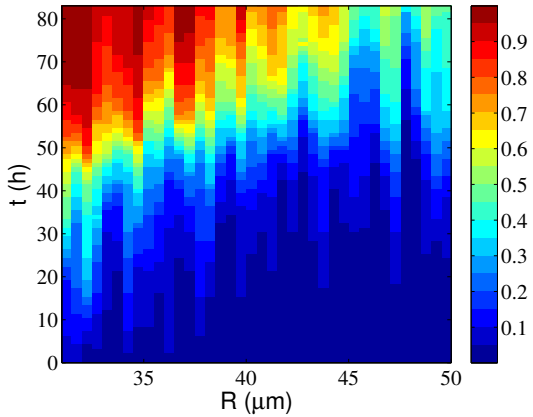
$f_c(R,t)$ fraction of patches of radius R closed at time t



$$f_c(R,t) = \mathrm{Prob}(t_c(R) \leq t) = 1 - \int_0^R p(R', t \mid R, 0)\, \mathrm{d}R'$$

Probabilistic description

$f_c(R,t)$ fraction of patches of radius R closed at time t



$$f_c(R,t) = \text{Prob}(t_c(R) \leq t) = 1 - \int_0^R p(R', t \mid R, 0)\, \mathrm{d}R'$$

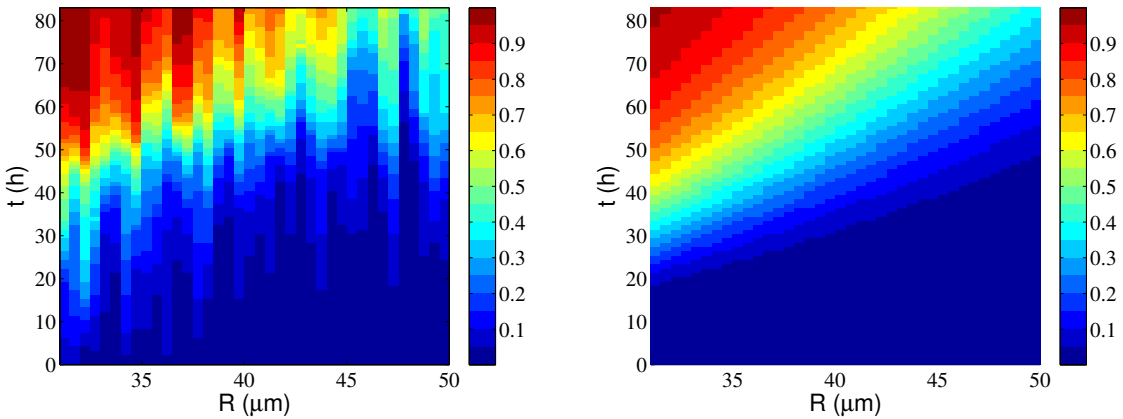
Backward Kolmogorov equation

$$\frac{\partial f_c}{\partial t} = -\frac{\gamma^*}{R}\frac{\partial f_c}{\partial R} + D\frac{\partial^2 f_c}{\partial R^2}$$

- R reflecting boundary
- 0 absorbing boundary

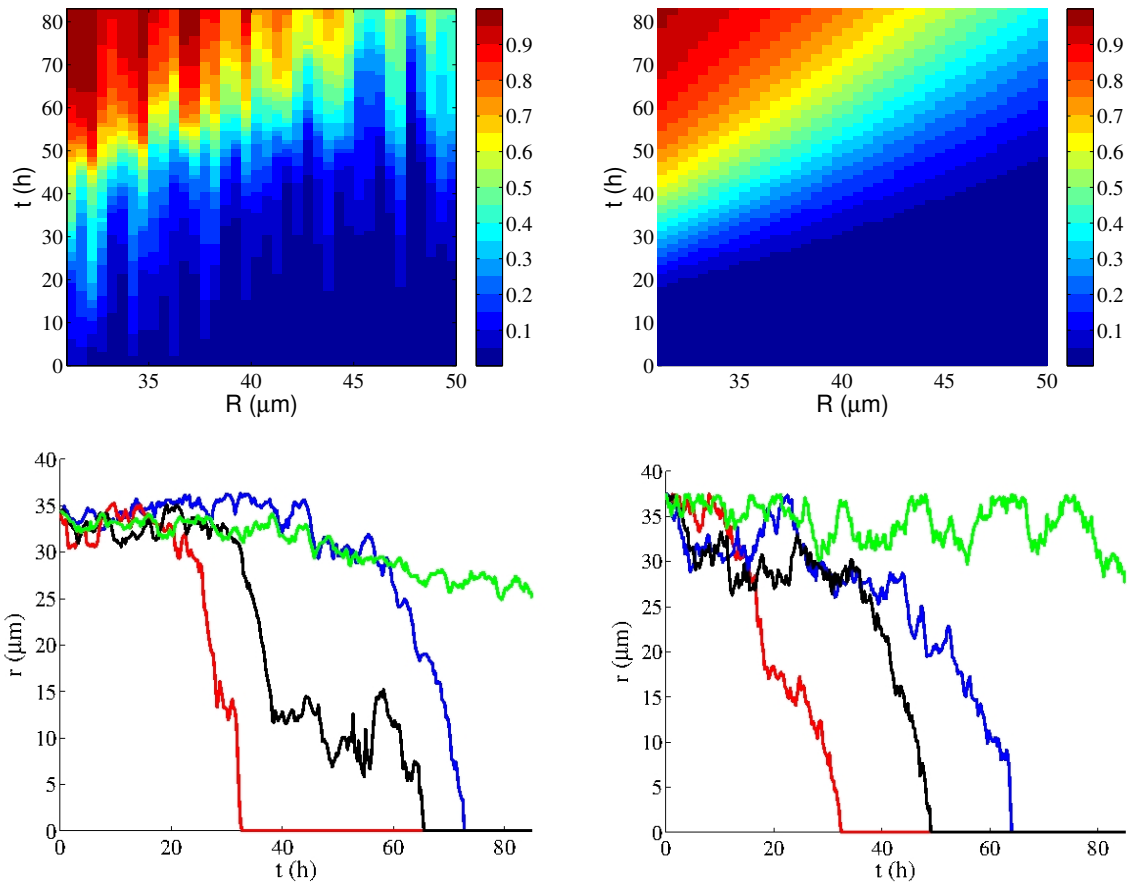
Least-squares fit

$$\begin{aligned} \gamma^* &= 10.0\,\mu\mathrm{m}^2\,\mathrm{h}^{-1} \quad [6, 13] \\ D &= 1.6\,\mu\mathrm{m}^2\,\mathrm{h}^{-1} \quad [0.5, 3.9] \end{aligned}$$



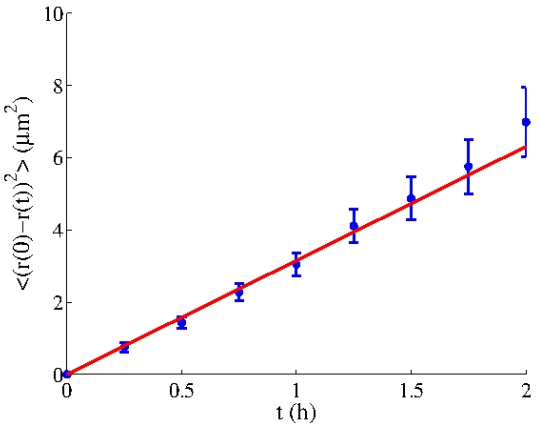
Least-squares fit

$$\gamma^* = 10.0\,\mu\mathrm{m}^2\,\mathrm{h}^{-1} \quad [6, 13]$$
$$D = 1.6\,\mu\mathrm{m}^2\,\mathrm{h}^{-1} \quad [0.5, 3.9]$$



Initial mean square deviation

Diffusive behaviour at early times



Model prediction

$$\langle (r(0) - r(t))^2 \rangle = 2D\,t$$

Linear regression $\Rightarrow$ $D = 1.5\,\mu\mathrm{m}^2\,\mathrm{h}^{-1}$ $\quad [1.0, 2.0]$

Alternative hypotheses

$$\dot{r} = -\frac{\gamma^*}{r} + \sigma^* + \sqrt{2\left(D + \frac{D_\gamma}{r^2}\right)}\,\eta(t)$$

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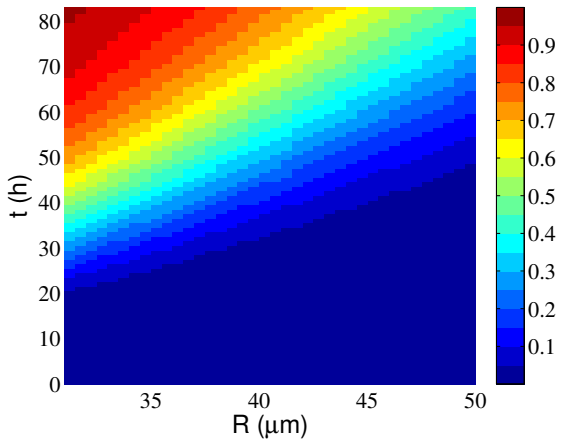
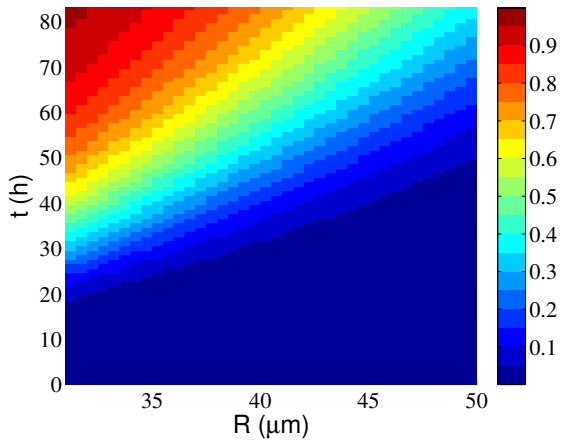
Tissue tension σ^*



Cable tension fluctuation D_γ



The following additional ingredients are negligible:

- Tissue tension: $\frac{\sigma^* R}{\gamma^*} \ll 1$
- Cable tension fluctuation: $\frac{D_\gamma}{DR^2} \ll 1$

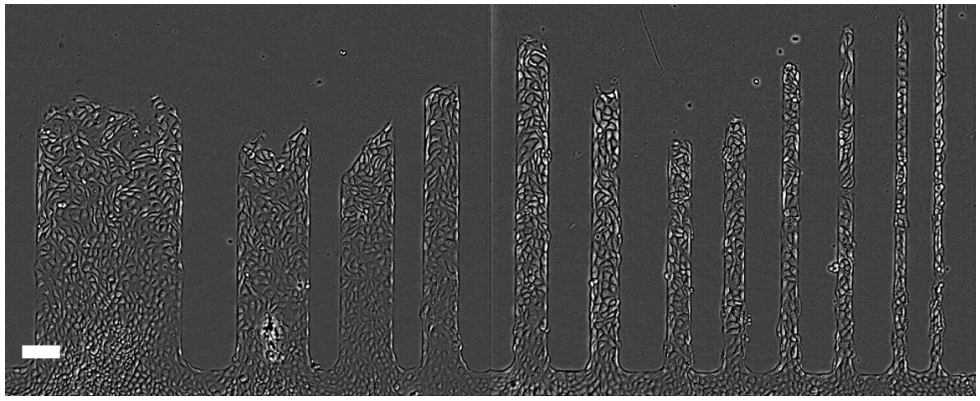
Conclusions

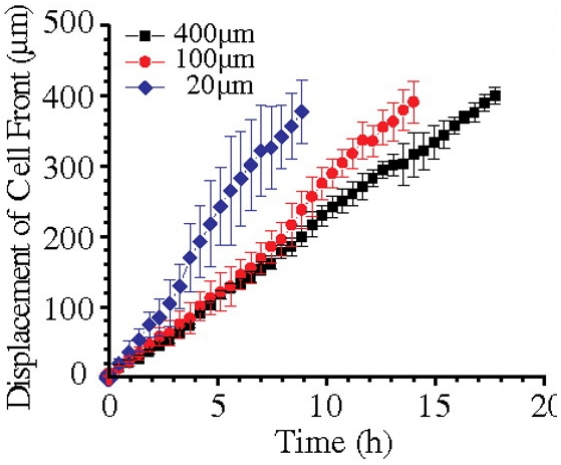
- cable contractility (line tension γ) dominates force generation
- noise cannot be neglected : $\frac{D}{\gamma^*} \simeq \frac{1}{6}$
- order of magnitude estimate of the friction coefficient
  $\gamma/\zeta \approx 10\,\mu\mathrm{m}^2\,\mathrm{h}^{-1}$ and $\gamma \approx 1$ nN $\Rightarrow \zeta \approx 10^2\,\mathrm{nN}\,\mu\mathrm{m}^{-2}\,\mathrm{s}$
- order of magnitude estimate of tension fluctuations
  $\Delta\sigma^2 = D\,\zeta^2 \approx 10^{-1}\,\mathrm{nN}^2\,\mu\mathrm{m}^{-2}\,\mathrm{h}$
  much larger than thermal fluctuations
  $\Delta\sigma^2_{\mathrm{thermal}} = \frac{k_B T}{2\pi R\,\xi} \approx 10^{-6}\,\mathrm{nN}^2\,\mu\mathrm{m}^{-2}\,\mathrm{h}$

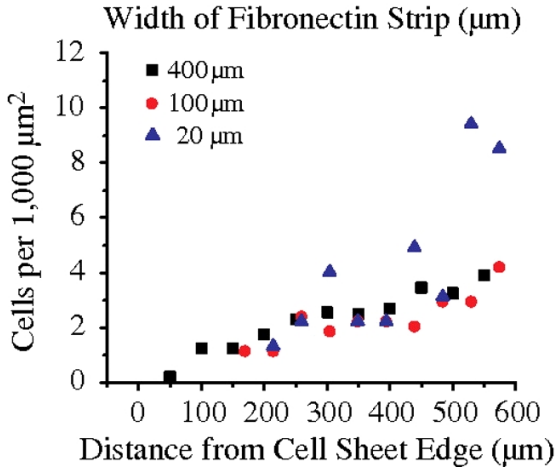
Nier et al., submitted (2014)

Outline

Collective cell migration along a channel







S.R.K. Vedula et al., PNAS (2012)

Model

- Geometry: 1D, $x \in [0\ L(t)]$
- Cell number balance: $\frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x}(\rho v) = -\frac{1}{\tau_{\text{div}}} \frac{\rho - \rho_{\text{div}}}{\rho_{\text{div}}} \rho$
- Constitutive equation: $\sigma = -p(\rho)$
- Momentum conservation: $\frac{\partial \sigma}{\partial x} = \xi\, v$

$$\Rightarrow v = \frac{1}{\xi} \frac{\partial \sigma}{\partial x} = -\frac{1}{\xi} p'(\rho) \frac{\partial \rho}{\partial x}$$

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- Boundary conditions
  - Front: $\sigma(x = L(t), t) = \sigma_{\text{p}}$
  - Back: $(\rho v)\,(x = 0, t) = 0$
  - Kinematic: $v(x = L(t), t) = \dot{L}(t)$

The Fisher-Kolmogorov equation

An equation of state $p(\rho) = E\,\ln(\rho/\rho_{\mathrm{el}})$

$$v = \frac{1}{\xi}\frac{\partial \sigma}{\partial x} = -\frac{E}{\xi}\frac{1}{\rho}\frac{\partial \rho}{\partial x} \Rightarrow \frac{\partial \rho}{\partial t} = \frac{E}{\xi}\frac{\partial^2 \rho}{\partial x^2} + \frac{1}{\tau_{\mathrm{div}}\rho_{\mathrm{div}}}\,\rho\,(\rho_{\mathrm{div}} - \rho)$$

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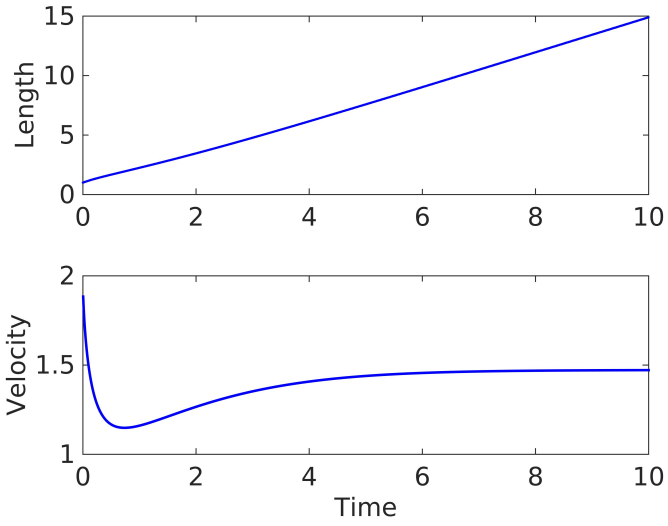
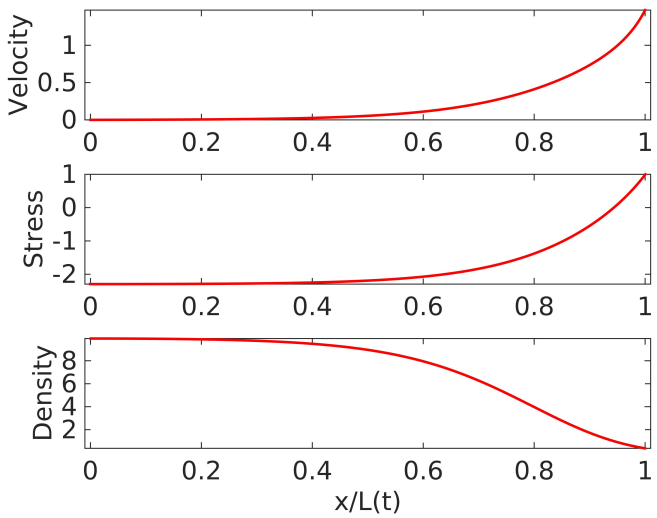
A propagating front

Leading edge

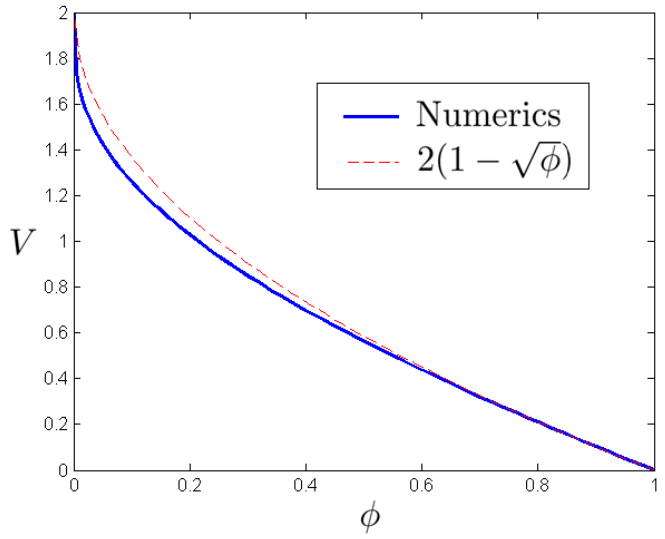


Profile



Front velocity

$$V = \sqrt{\frac{E}{\xi\,\tau_{\mathrm{div}}}}\; F\left[\frac{\rho_{\mathrm{el}}}{\rho_{\mathrm{div}}}\, e^{-\frac{\sigma_{\mathrm{p}}}{E}}\right]$$



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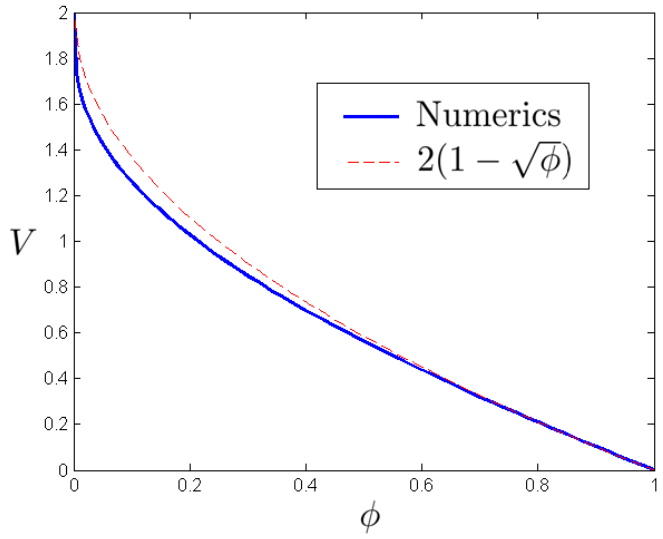

Order of magnitude $\quad V \approx 10^{0}\ \mu\mathrm{m\,h^{-1}}$

- $E \approx 10^{3}\ \mathrm{Pa}$
- $\xi \approx 10^{-2}\ \mathrm{Pa\,m^{-2}\,s}$
- $\tau_{\mathrm{div}} \approx 10^{4}\ \mathrm{s}$

Influence of viscosity?

$$\sigma = -E \ln(\rho/\rho_{\mathrm{el}}) + \eta \frac{\partial v}{\partial x}$$

Dimensionless viscous coefficient

$$\tilde{\eta} = \frac{\eta}{E\,\tau_{\mathrm{div}}} \approx \frac{10^5}{10^3\,10^4} \approx 10^{-2}$$

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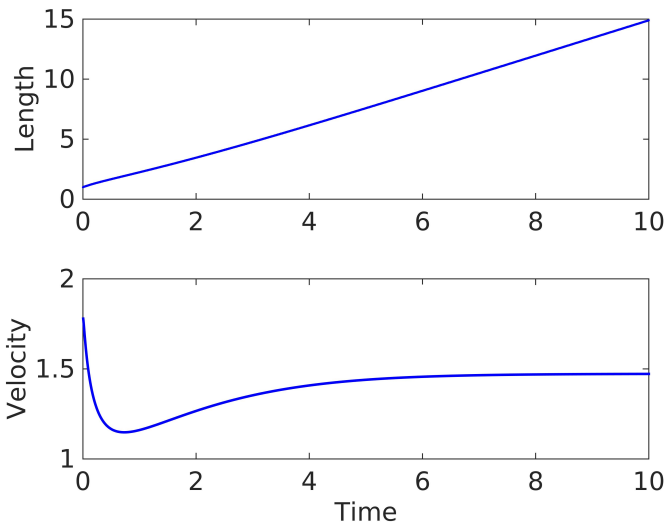
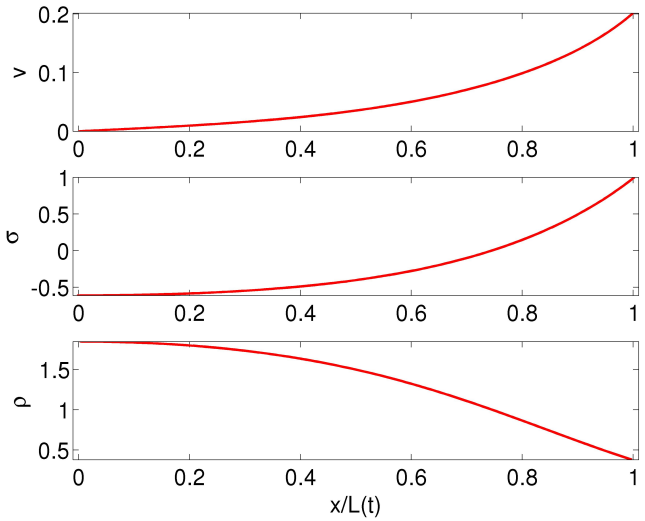
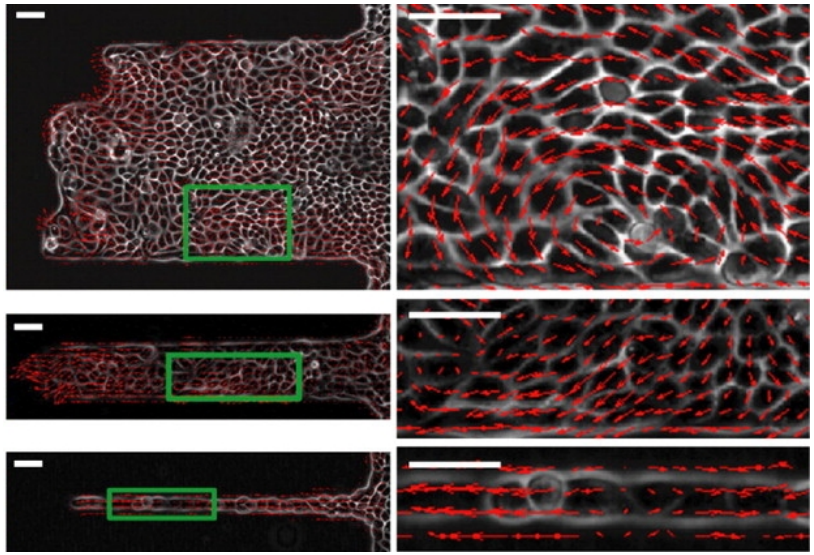


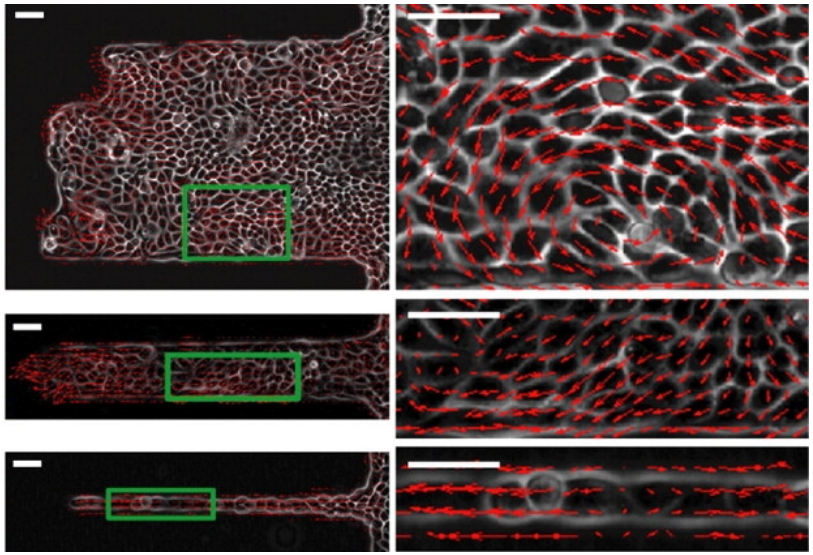
Profile

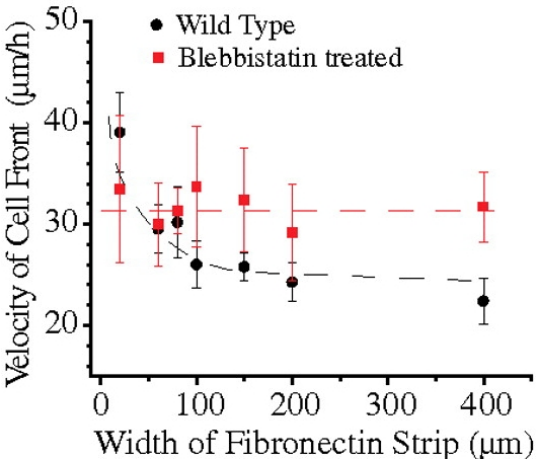


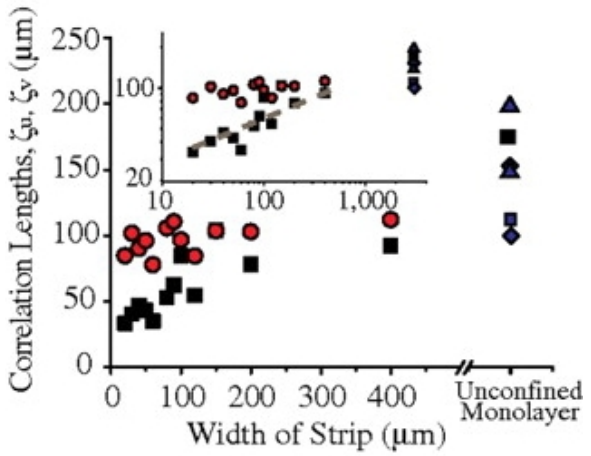
Extension to 2D: dependence on confinement



Extension to 2D: dependence on confinement

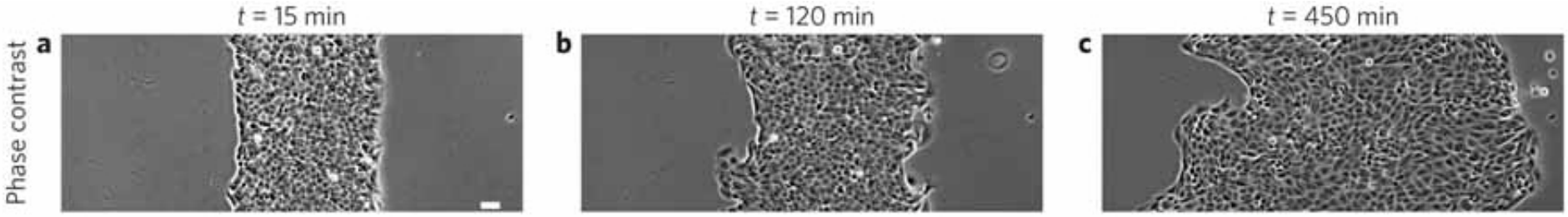


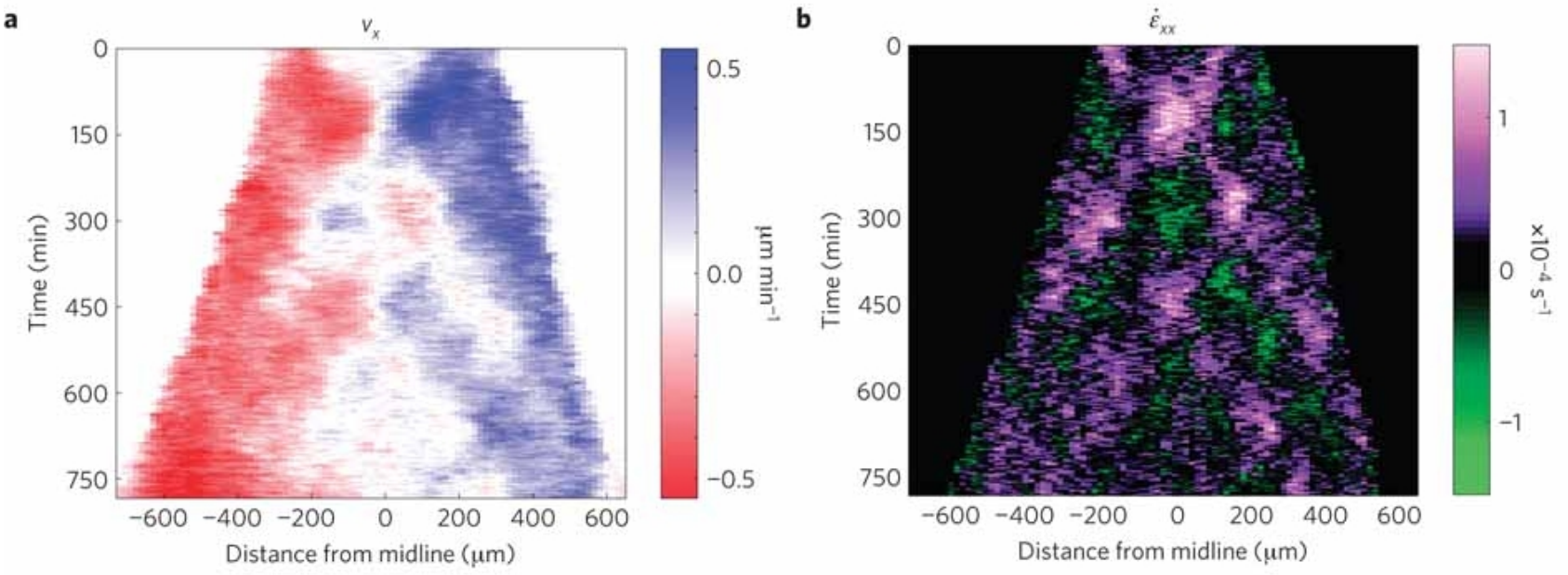




S.R.K. Vedula et al., PNAS (2012)

Propagating waves





How to include active motility?

X. Serra-Picamal et al., Nat. Phys. (2012)

Conclusion: collective cell migration

- experimental tests?
- how to model cell contractility and bulk cell motility?
- how can a propagating wave solution become unstable?
- *in vivo* collective cell migration?

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