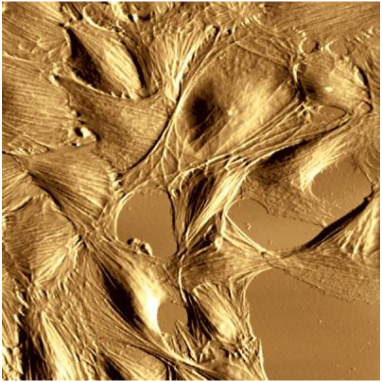
Mechanics of contractile actomyosin bundles

J.F. Joanny [1] P. Marcq [1] J. Prost [1] N. Yoshinaga [2]

[1]Physico-Chimie Curie, Institut Curie, Paris

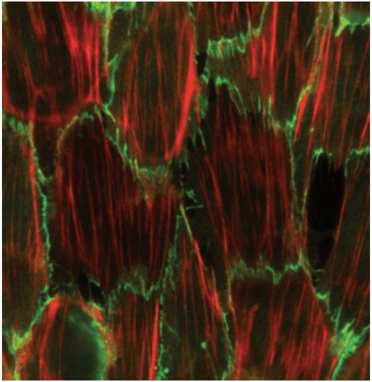
[2]WPI Advanced Institute for Materials Research, Tohoku University, Sendai

Contractile actomyosin bundles



Fibroblasts

Swiss Nanoscience Institute

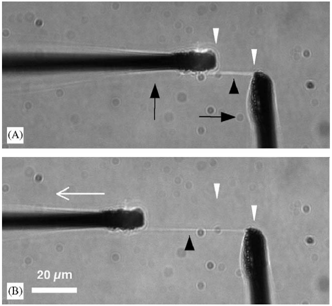


Arterial endothelial cells

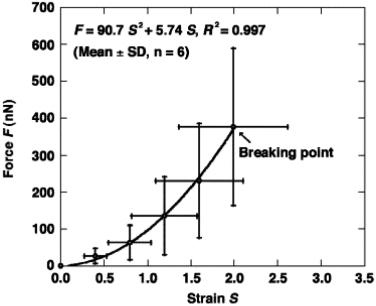
Kaunas et al., PNAS (2005)

Elastic modulus of a stress fiber

Pulling on a stress fiber



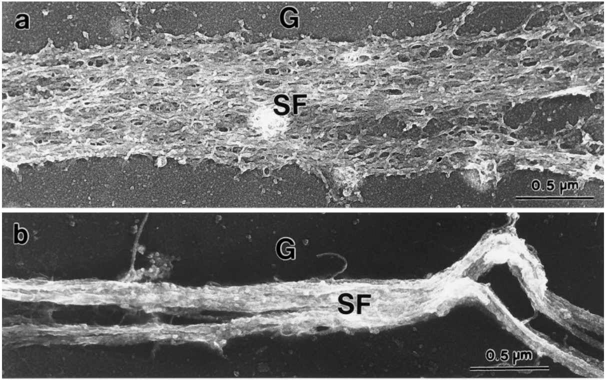
Force-extension data



- 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 (constant material content)
- 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

Outline

1. What determines the contraction time scale of actomyosin bundles after laser ablation?

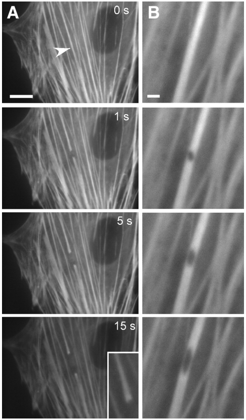
2. Why do actin filaments exhibit ordered polarity patterns in actomyosin bundles?

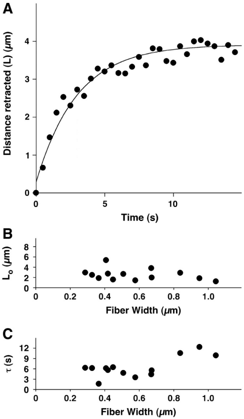
Outline

1. What determines the contraction time scale of actomyosin bundles after laser ablation?

2. Why do actin filaments exhibit ordered polarity patterns in actomyosin bundles?

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

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

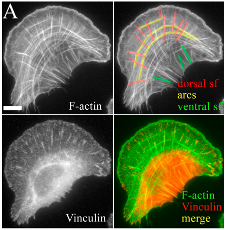
Dissipation due to protein friction

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

Dynamic proteins

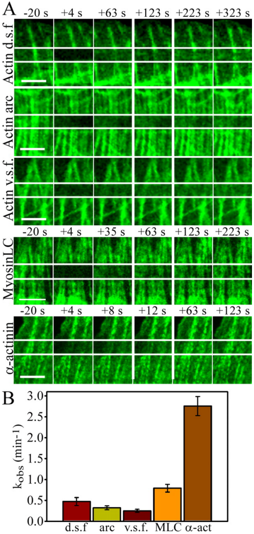
FRAP experiments

Fluorescence **R**ecovery **A**fter **P**hotobleaching



- 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

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

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

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

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

Contraction time

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

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

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

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

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

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

Poroelasticity

Gel swelling/shrinking dynamics explained by

- permeation of (liquid) solvent (pressure $p(z,t)$)
- in the (elastic) polymer network (displacement $u(z,t)$)

Force balance (E elastic modulus)

$$E\frac{\partial^2 u}{\partial z^2} = \frac{\partial p}{\partial z}$$

Darcy's law (κ hydraulic permeability)

$$\frac{\partial u}{\partial t} = \kappa\frac{\partial p}{\partial z}$$

$\Rightarrow$ Diffusion equation with diffusion constant $D = \kappa E$

$$\frac{\partial u}{\partial t} = D\,\frac{\partial^2 u}{\partial z^2}$$

Poroelastic contraction: a diffusive time

Stress fiber $\tau_D \propto \frac{a_0^2}{D} \simeq \frac{a_0^2}{\kappa E}$ with $\kappa \propto \frac{\xi^2}{\eta_c}$

- $a_0 \approx 0.1\ \mu\text{m}$ bundle radius
- $\xi \approx 10$ nm mesh size
- $\eta_c \approx 10^{-3} - 10^{-1}$ Pa s solvent viscosity
- $E \approx 10^5 - 10^6$ Pa elastic modulus

$$\tau_D \propto \left(\frac{a_0}{\xi}\right)^2 \frac{\eta_c}{E} \approx 10^{-6} - 10^{-4}\ \text{s}$$

Cross-over radius $\tau \approx \tau_D$

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

- $a_0 \ll a_c$: viscoelasticity dominates (*in vivo*)
- $a_0 \gg a_c$: poroelasticity dominates (*in vitro*?)

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

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

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!

Active stress

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

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

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

Active stress

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

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

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

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

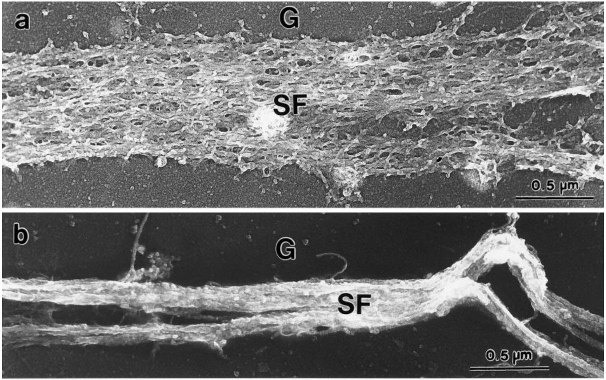
Exact solution

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.

Stress fibers: active contractility



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

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

When the initial state differs from the elastic reference state

Contraction with two time scales $\tau_K = \frac{\eta_p}{3K}$ and $\tau_G = \frac{\eta_p}{2G}$.

$$\frac{a(t) - a_{\text{ref}}}{a_{\text{ref}}} = -\frac{\sigma_A}{3K}\left(1 - e^{-\,t/\tau_K}\right) + u_K\, e^{-\,t/\tau_K} + u_G\, e^{-\,t/\tau_G},$$

$$\frac{L(t) - L_{\text{ref}}}{L_{\text{ref}}} = -\frac{\sigma_A}{3K}\left(1 - e^{-\,t/\tau_K}\right) + e_K e^{-\,t/\tau_K} + e_G\, e^{-\,t/\tau_G}.$$

Measurement of the Poisson ratio?

$$\frac{\tau_K}{\tau_G} = \frac{1 - 2\nu}{1 + \nu}$$

General case: an active visco-poroelastic material

Generalized diffusion equation

When the initial state is the elastic reference state:

$$\frac{a(t)-a_0}{a_0} = \frac{L(t)-L_0}{L_0} = -\frac{\sigma_A}{3K} + \sum_n e_n\, e^{-\,t/\tau_n}$$

The relaxation times τ_n are the solutions of:

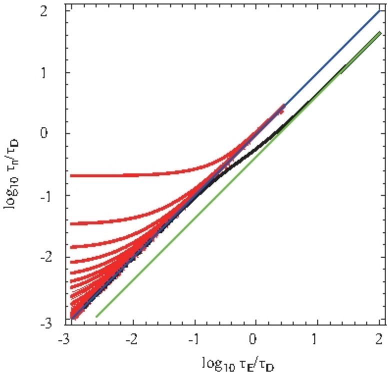
- $\left(\frac{\tau_E}{\tau_n}-1\right)\,\left[\frac{a_0}{l_n}\,J_1'\left(\frac{a_0}{l_n}\right)-\frac{1}{3}\,J_1\left(\frac{a_0}{l_n}\right)\right]=\frac{4}{3}\,\frac{\nu}{1-\nu}\,J_1\left(\frac{a_0}{l_n}\right)$, when $\tau_n > \tau_E$;
- $\left(\frac{\tau_E}{\tau_n}-1\right)\,\left[\frac{a_0}{l_n}\,I_1'\left(\frac{a_0}{l_n}\right)-\frac{1}{3}\,I_1\left(\frac{a_0}{l_n}\right)\right]=\frac{4}{3}\,\frac{\nu}{1-\nu}\,I_1\left(\frac{a_0}{l_n}\right)$, when $\tau_n < \tau_E$,

with $l_n^2 = D\,|\tau_E-\tau_n|$, $\tau_E = \frac{(1+\nu)(1-2\nu)}{1-\nu}\,\frac{\eta_p}{E}$.

Well-defined limits

- $\tau_E \gg \tau_D$: viscoelastic limit ($a_0 \ll a_c$)
- $\tau_E \ll \tau_D$: poroelastic limit ($a_0 \gg a_c$)

General case: relaxation times τ_n



$\tau_n > \tau_E$: $y > x$

blue line: $y = x$

$\tau_n < \tau_E$: $y < x$

green line: $\tau_n = \tau_K$

- $\frac{\tau_E}{\tau_D} \ll 1$: poroelastic limit
- $\frac{\tau_E}{\tau_D} \gg 1$: viscoelastic limit

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 yield
  - → the order of magnitude of τ
  - → the order of magnitude of σ_A
- Cross-over to visco-poroelasticity when

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

- Exact solution of an active visco-poroelastic model, and its limits
- Obvious need for more quantitative data
  - reconstituted bundles?

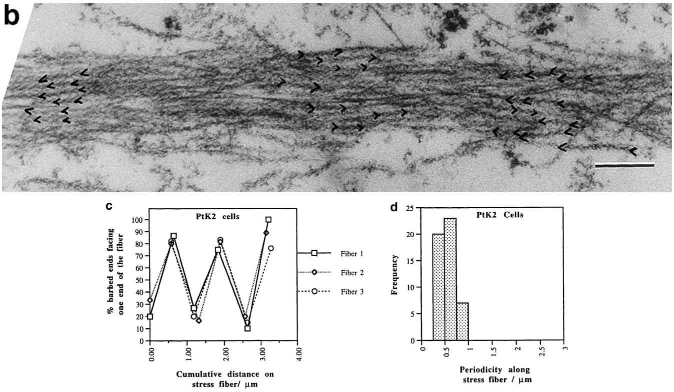
Yoshinaga and Marcq, Phys. Biol. (2012)

Outline

1. What determines the contraction time scale of actomyosin bundles after laser ablation?

2. Why do actin filaments exhibit ordered polarity patterns in actomyosin bundles?

A polar structure: alternating polarity

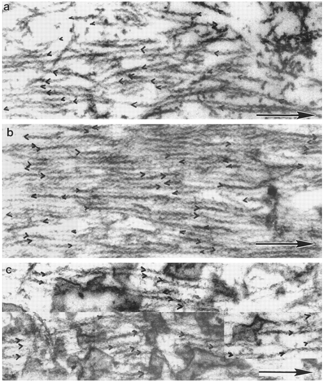


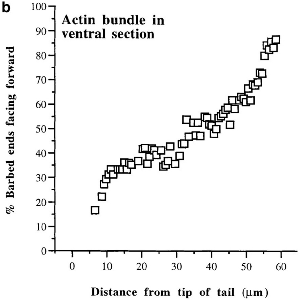
- Ptk2 cells (kidney epithelium), bar: 0.2 μm
- Actin decorated with S1 myosin heads
- Wavelength $\lambda \simeq 1\ \mu m$

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)

Relevant variables

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

- Mesoscopic average of the polarity of actin filaments
- F-actin barbed ends face focal adhesions
- Boundary conditions:

$$p(0,t) = -1 \qquad p(L,t) = +1$$

Longitudinal strain $e(z,t)$

Stress fiber as a 1D active polar elastomer

Theoretical description of a stress fiber...

- on mesoscopic scales
- in 1D
- as a one-component system
- active
- elastic $t \gg \tau_{\text{viscoelastic}}$
- polar
- without turn-over $t \gg \tau_{\text{turn-over}}$

using linear irreversible thermodynamics

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

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

Constitutive equations

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.

Couplings between fluxes and forces

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

A stationary bifurcation

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

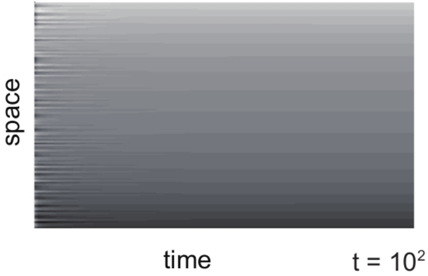
Bifurcation point $D = 0$ when $\frac{\beta\Delta\mu}{w} = \frac{KG}{w^2} - 1$

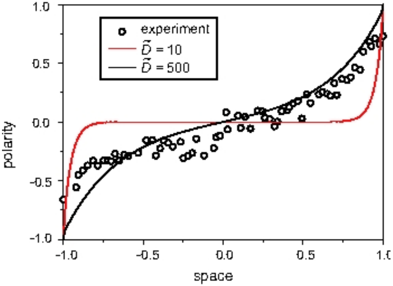
Graded polarity pattern $D > 0$

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

Dimensionless equation

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





Negative diffusion $D < 0$ when $\frac{\beta\Delta\mu}{w} > \frac{KG}{w^2} - 1$

Damped Kuramoto-Sivashinsky equation

Stabilizing higher-order elastic term $\nu/2\ \left(\partial_z^2 p\right)^2$ in the free energy

$$\frac{\partial p}{\partial t} + \alpha\Delta\mu\, p\, \frac{\partial p}{\partial z} = -\frac{a}{\gamma}\, p + D\, \frac{\partial^2 p}{\partial z^2} - \frac{\nu}{\gamma}\, \frac{\partial^4 p}{\partial z^4}$$

For large enough damping: stable periodic stationary solutions

Dimensionless equation

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

with $\tilde{t} = \frac{a}{\gamma}t$, $\tilde{z} = \frac{a}{\alpha\gamma\,\Delta\mu}z$, $\tilde{D} = \frac{aD}{(\alpha\gamma\Delta\mu)^2}$, $\tilde{\nu} = \frac{\nu}{a}\left(\frac{a}{\alpha\gamma\Delta\mu}\right)^4$

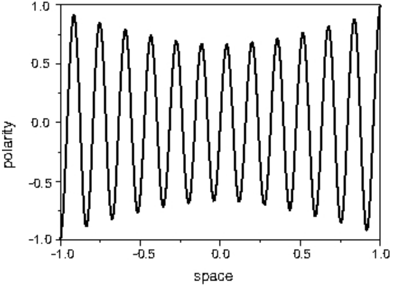
Alternating polarity pattern $D < -2\sqrt{\tilde{\nu}}$

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

Alternating pattern when $\tilde{D} < -2\sqrt{\tilde{\nu}}$ with 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

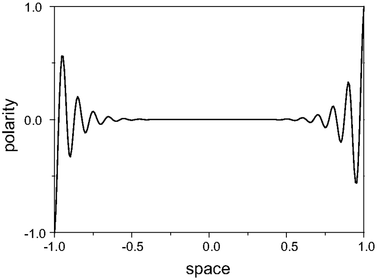


A new type of polarity pattern

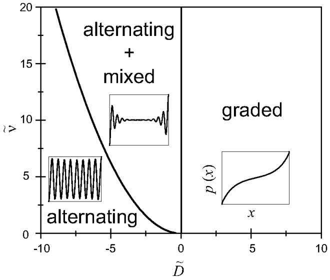
$$\frac{\partial p}{\partial \tilde{t}} + p\frac{\partial p}{\partial \tilde{z}} = -p + \tilde{D}\,\frac{\partial^2 p}{\partial \tilde{z}^2} - \tilde{\nu}\frac{\partial^4 p}{\partial \tilde{z}^4}$$

Mixed polarity $p(z) = 0$ is stable when $-2\sqrt{\tilde{\nu}} < \tilde{D} < 0$.

- mixed polarity in the bulk
- alternating polarity close to the boundaries.



Phase diagram



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.

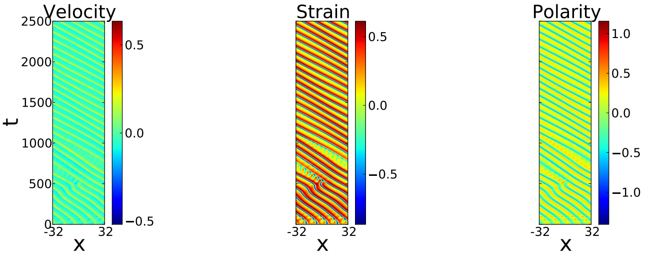
  $$\lambda^{-2} = a + b\, \Delta\mu$$
  $$\lambda^{-2} = c + d/G$$

- The bifurcation also occurs for viscoelastic materials.

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

Secondary bifurcation: propagating waves

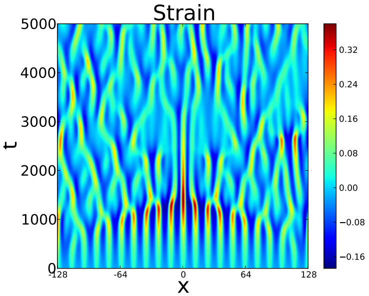
Rheology: (Maxwell) viscoelastic liquid



Here with periodic boundary conditions: rotating ring

Possible applications

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


Strain
5000
4000
3000
2000
1000
0
t
-128
-64
0
64
128
x
0.32
0.24
0.16
0.08
0.00
−0.08
−0.16

Thank you!