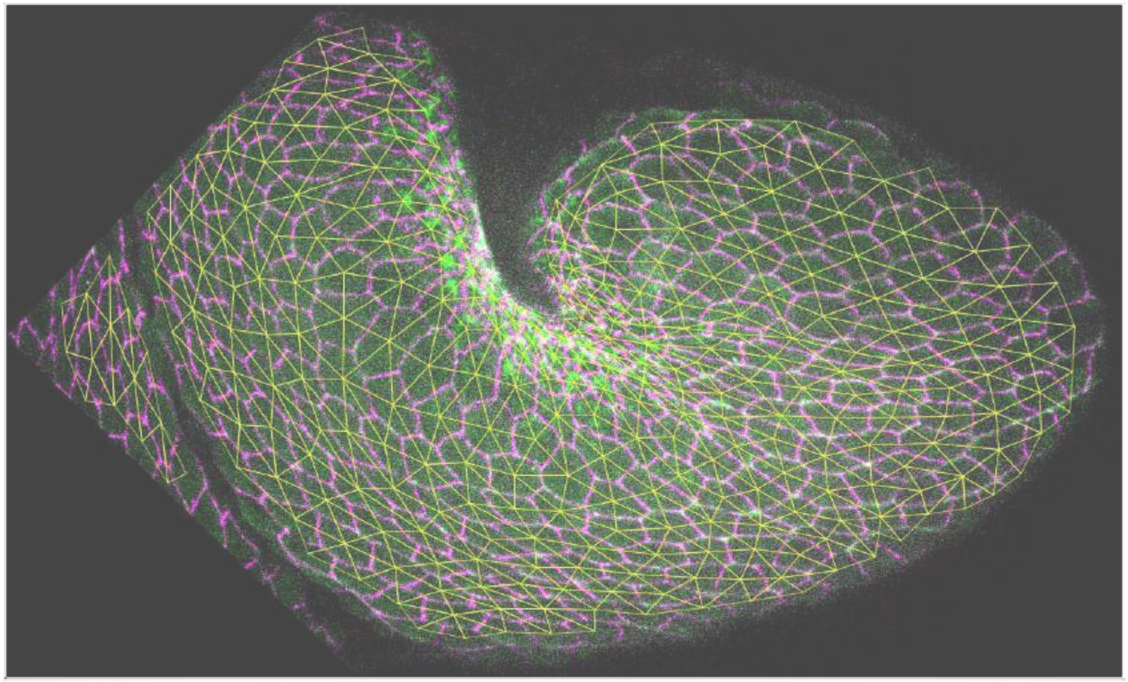
Morphogenesis: space, time, information



Course 3: Spatial and temporal instabilities

Thomas Lecuit

chaire: Dynamiques du vivant

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Biological organisation in space and time

- Two modalities of information flow during morphogenesis

Program

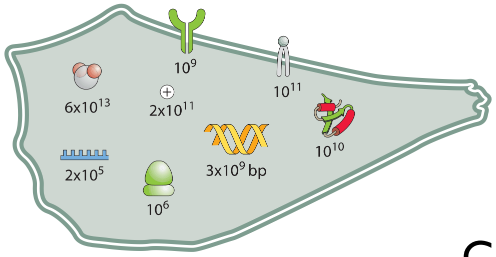
- hierarchical, indirect interactions
- modular
- long and short range interactions
- high-wired
- multiple parameters

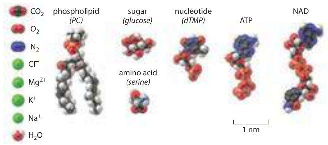
Self-organization

- local and direct interactions
- few rules and parameters

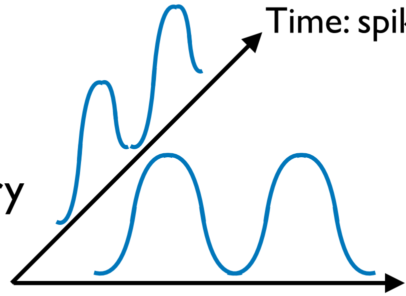
Spatial and Temporal Instabilities

Chemical and Mechanical Information



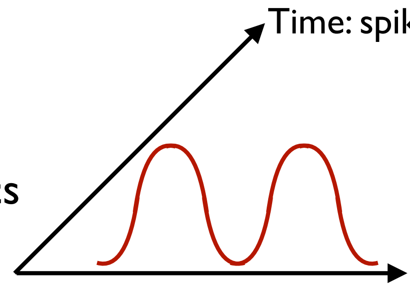


Chemistry



self-organization in nonequilibrium chemical systems

Mechanics



self-organization in nonequilibrium mechanical systems

Chemistry → Mechanics

self-organization in nonequilibrium mechano-chemical systems

Chemistry ⇄ Mechanics

1. Introduction - Program and Self-Organisation

2. Chemical Instabilities

21. Spatial instabilities - Turing patterns
22. Temporal instabilities - Excitability
23. Spatial-temporal instabilities: waves

3. Mechanical instabilities

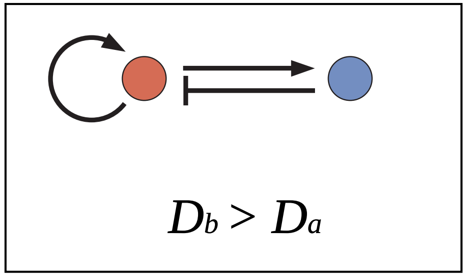
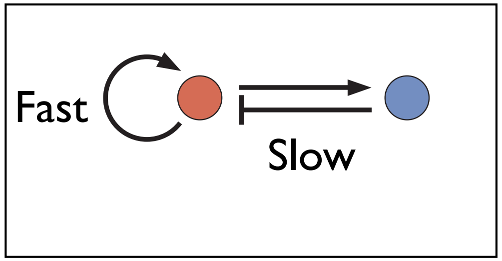
31. Cellular aggregates: viscoelastic model
32. Active gel: hydrodynamic and viscoelastic models

4. Mechano-chemical Instabilities

41. Mechano-chemical coupling: actomyosin dynamics
42. Actin based trigger waves

5. Developmental significance: impact on cellular and tissue morphogenesis

Summary: Spatial and temporal instabilities I — 27 Nov

	Spatial Instabilities	Temporal Instabilities
	• Local positive feedback • Long range inhibition	• Local positive feedback • Negative feedback with a delay
Chemical		

Mechanical

Contractility driven positive feedback
Elasticity: « long-range inhibitor »

Turing-like patterns

III - Mechanical Instabilities

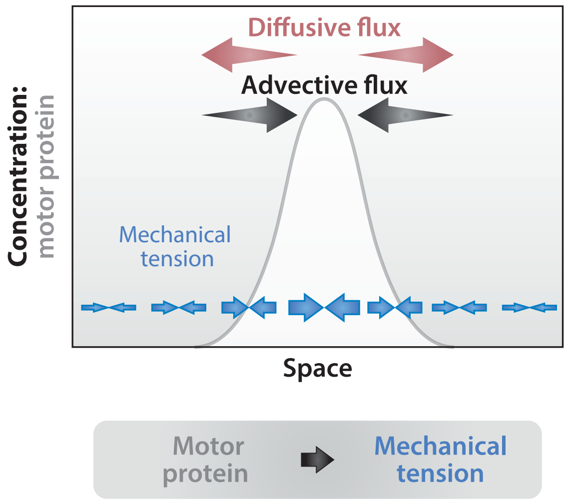
- Pattern formation in an active fluid (e.g. actomyosin gel)

$$\partial_t c = -\partial_x j, \qquad j = -D\partial_x c + vc, \qquad (1)$$

diffusion advection

Diffusion: smoothens fluctuations

Advection: amplifies fluctuations (mechanical feedback)



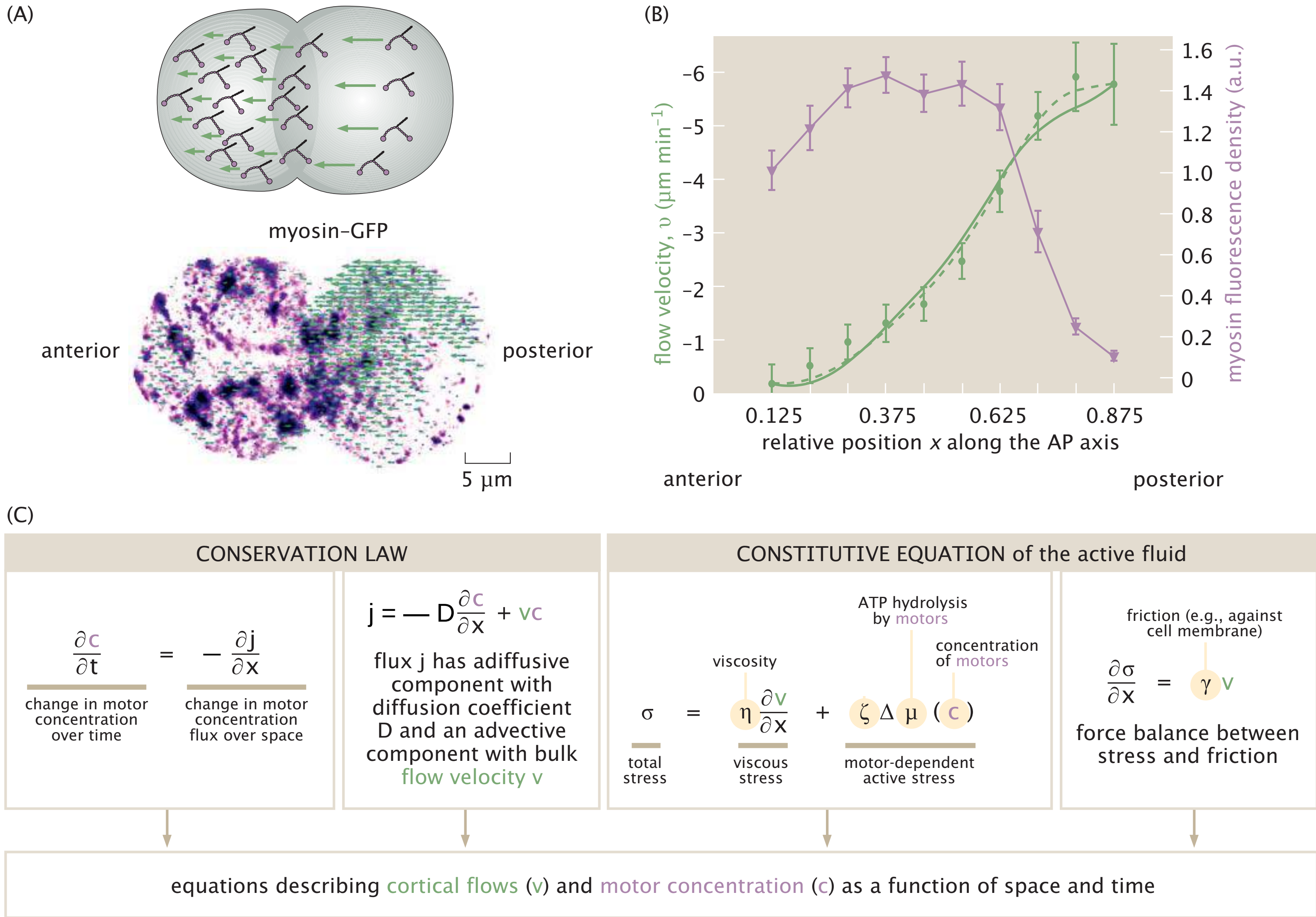
- Dimensionless parameter that considers the respective contributions of two sources of flux

  Péclet number (advection rate/diffusion rate)

$$\mathrm{Pe} = U\ell/D$$

III - Mechanical Instabilities

- Pattern formation in an active fluid: actomyosin flow



M. Mayer et al., and SW. Grill. *Nature*. 2010. 467, 617-621
illustration: Nigel Orme

III - Mechanical Instabilities

- Pattern formation in an active fluid (e.g. actomyosin gel)

Hydrodynamic flow description:

$\partial_t c = -\partial_x j, \qquad j = -D\partial_x c + vc,$ (1) conservation law (species *c*)

diffusion advection

$\sigma = \eta\partial_x v + \zeta\Delta\mu.$ (2) constitutive equation

$\partial_x \sigma = \gamma v,$ (3) force balance

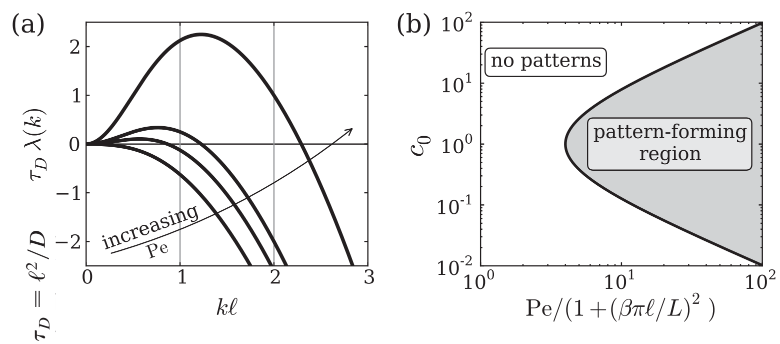
Linear stability: Eigen values $\lambda(k) = -k^2 D\left(1 - \frac{\mathrm{Pe}c_0\partial_c f(c_0)}{1+k^2\ell^2}\right).$ Flow driven non-homogeneity for $\frac{\mathrm{Pe}c_0\partial_c f(c_0)}{1+(\beta\pi\ell/L)^2} > 1.$

$\ell \equiv \sqrt{\eta/\gamma}$ hydrodynamic length scale

$\mathrm{Pe} = U\ell/D$ Péclet number (advection rate/diffusion rate)

$\zeta\Delta\mu(c) = (\zeta\Delta\mu)_0 f(c)$ with $\partial_c f(c_0) > 0$ (active stress increases with concentration of c_0)

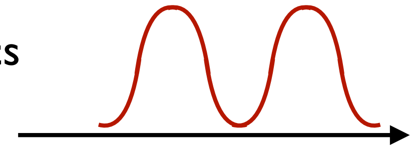
- Active stress driven flow must overcome frictional resistance and diffusive dispersion: (requires large enough *Pe* and upregulation of active stress by regulator $\partial_c f(c_0)>1$)



J. Bois, F. Jülicher and SW. Grill. *PRL*. 2011. 106, 028103

Mechanical instabilities

Mechanics

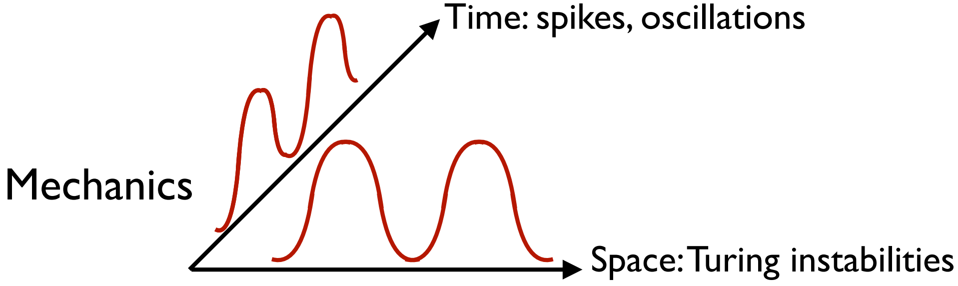


self-organization in nonequilibrium mechanical systems

- Turing like pattern: Activator induced active stress drives fluid flow that must overcome frictional resistance and diffusion.
- Active stress as « local activator» with autocatalysis (advective flow) Friction as « long range inhibitor ».

III - Mechanical Instabilities

Temporal Mechanical instabilities



self-organization in nonequilibrium mechanical systems

III - Mechanical Instabilities

- Pulsatory patterns in active fluids (e.g. actomyosin gel)

<u>Reaction-Diffusion-Advection Model:</u>

Hydrodynamic flow description with **2 chemical species that activate or inhibit active stress**

$$\partial_t A = -\nabla \cdot (\mathbf{v}A) + D\nabla^2 A, \qquad (1)$$

$$\partial_t I = -\nabla \cdot (\mathbf{v}I) + \alpha D\nabla^2 I, \qquad (2) \qquad \alpha = D_I/D$$

$$\nabla \cdot \sigma = \gamma \mathbf{v}, \qquad \sigma = \sigma_p + \zeta\Delta\mu \mathbb{1}. \qquad (3)$$

σ_p: passive/viscous stress

$\zeta\Delta\mu\mathbb{1}$: active stress (function of A and I)

$\zeta\Delta\mu = (\zeta\Delta\mu)_0 f(\mathbf{c})$. with $f(\mathbf{c}) = f_0 + (1+\beta)\frac{A}{A+A_s} + (1-\beta)\frac{I}{I+I_s}$,

β asymmetric parameter

β >1: A activates and I inhibits active stress

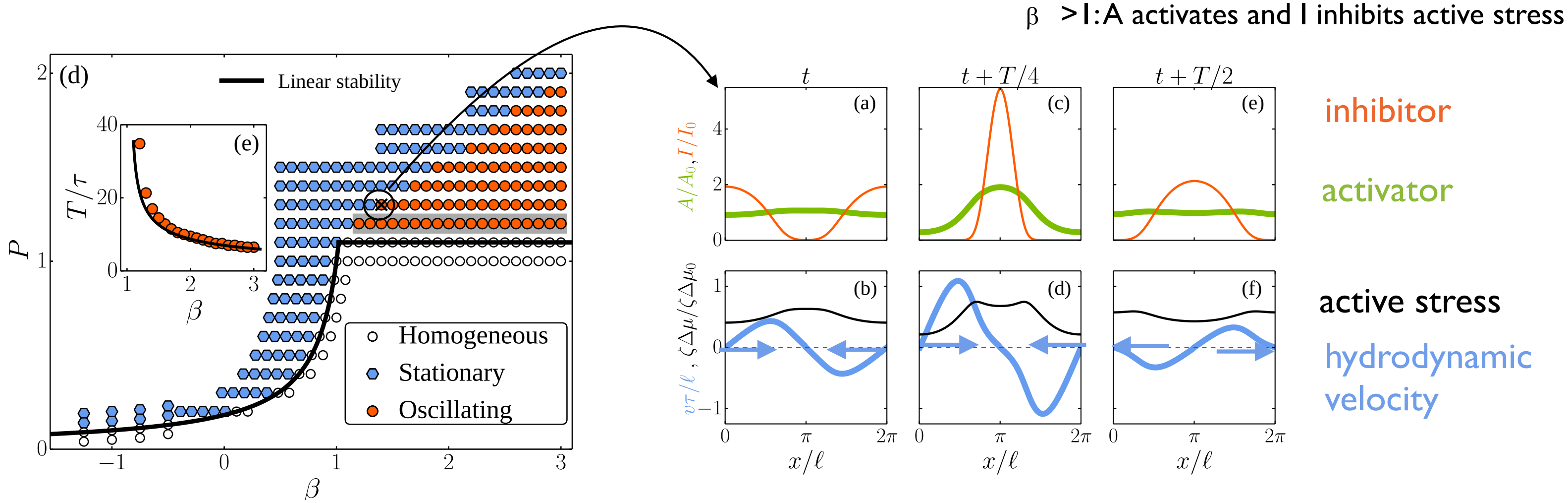
Pulsatory dynamics emerge:

1. if activator of active stress A diffuses faster than inhibitor I

(different diffusive relaxation time scale)

P: Péclet number

$P = v.L/D$



K. Vijay Kumar, J. Bois, Frank Jülicher and Stephan Grill. *PRL.* (2014). 112, 208101

III - Mechanical Instabilities

- Pulsatory patterns in active fluids (e.g. actomyosin gel)

<u>Reaction-Diffusion-Advection Model:</u>

Hydrodynamic flow description with **2 chemical species**

$$\partial_t A = -\nabla \cdot (\mathbf{v}A) + D\nabla^2 A - \kappa(A - A_0), \qquad (12)$$

$$\partial_t I = -\nabla \cdot (\mathbf{v}I) + D\nabla^2 I - \rho\kappa(I - I_0), \qquad (13)$$

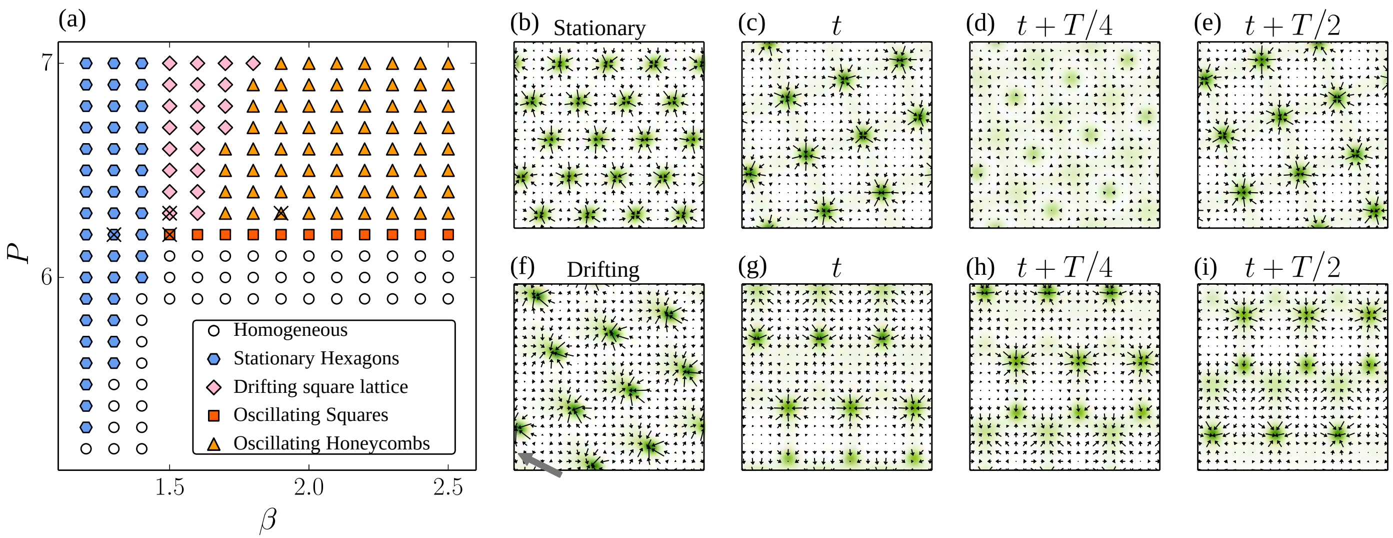
κ activator turnover rate

$\rho > 0$ ratio of inhibitor to activator turnover rate

Pulsatory dynamics emerge:

2. if activator of active stress turns over faster than inhibitor

(different kinetic relaxation time scales)



K. Vijay Kumar, J. Bois, Frank Jülicher and Stephan Grill. *PRL.* (2014). 112, 208101

III - Mechanical Instabilities

- Pulsatory patterns in active fluids (e.g. actomyosin gel)

Active stress regulated by Activator A and Inhibitor I: $\sigma_a = \sigma_a(c_A, c_I)$

Pulsatory dynamics emerges from coupling between:

- differential effect of A and I on active stress generation
- differential relaxation modes of A and I (diffusion or turnover)

Active stress also depends on density and orientational order of actin filaments and MyosinII minifilaments: allows for more complex feedbacks and patterns of orientational order of actomyosin network

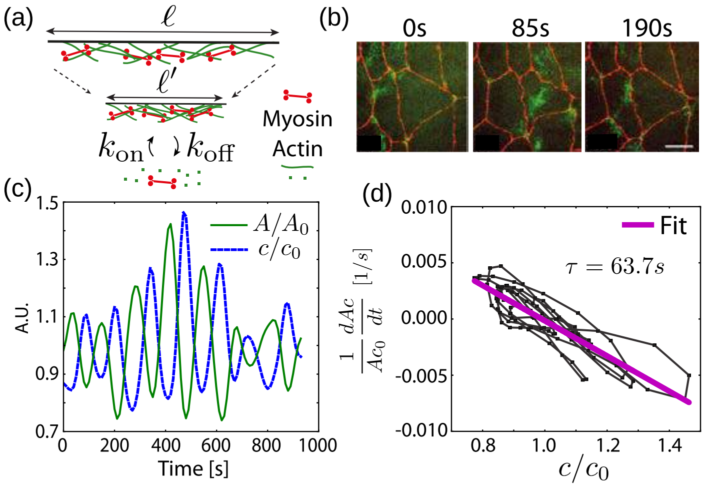
K. Vijay Kumar, J. Bois, Frank Jülicher and Stephan Grill. *PRL*. (2014). 112, 208101

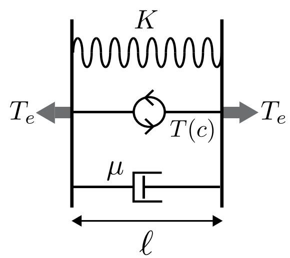
- Pulsatory patterns in viscoelastic contractile networks

Model: Contractile viscoelastic network with turnover :

Captures properties of actomyosin networks in cells.

$$k_{\mathrm{on}} = c_0/\tau$$
$$k_{\mathrm{off}} c = c/\tau$$





turnover

mass conservation ($dcl/dt = 0$ if no turnover)

$$\frac{dc}{dt} = -\frac{1}{\tau}(c - c_0) - \frac{c}{l}\frac{dl}{dt}, \qquad (1)$$

$$\mu \frac{dl}{dt} = T_e - T(c) - K(l), \qquad (2)$$

viscous force

external force

contractile force

elastic force

Kai Dierkes, A. Sumi, J. Solon and Guillaume Salbreux. PRL, (2014)113, 148102.

III - Mechanical Instabilities

- Pulsatory patterns in viscoelastic contractile networks

Model: Contractile viscoelastic network with turnover : $\mu \frac{dl}{dt} = T_e - T(c) - K(l),$ (2)

- linear stability analysis:
steady state c_0, l_0 $T(c) = T(c_0) + t_1(c - c_0)$
$K(l) = K(l_0) + k_1(l - l_0) + k_3(l - l_0)^3$

→ Hopf bifurcation for:
$(t_1 c_0)/(k_1 l_0) = 1 + \mu/(k_1 \tau)$

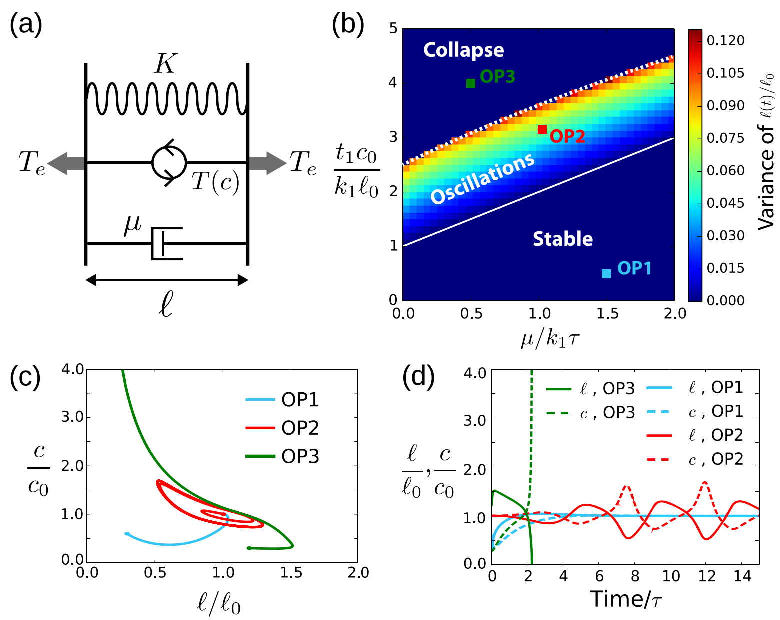
- Significance:

Contraction t_1 concentrates contractile units thereby increasing contraction: **Positive Feedback**

Viscous damping opposes (and elastic tension enhances) this effect. μ/k_1: relaxation/retardation time scale

Constant turnover tends to restore c to c_0 and down regulate contraction: **Negative Feedback**

τ : turnover time scale



Oscillatory dynamics emerges when:
- contraction overcomes viscous resistance and motor turnover

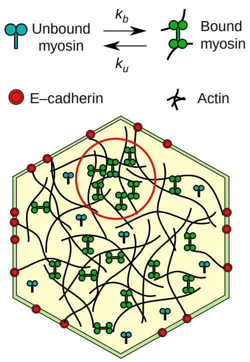
Kai Dierkes, A. Sumi, J. Solon and Guillaume Salbreux. PRL, (2014)113, 148102.

III - Mechanical Instabilities

- Pulses, travelling waves and contractile instabilities in viscoelastic contractile networks

<u>Model: Contractile viscoelastic network with turnover of actin and MyosinII:</u>

- Study the effects of non-linearities associated with:
  - active stress (function of network density, orientational order)
  - elastic energy (function of MyoII and actin densities)
  - turnover (MyoII strain dependent unbinding)

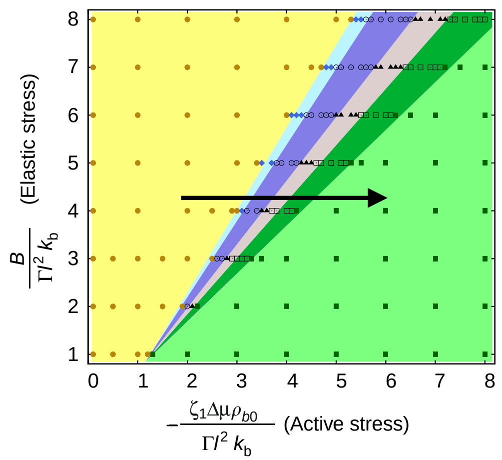


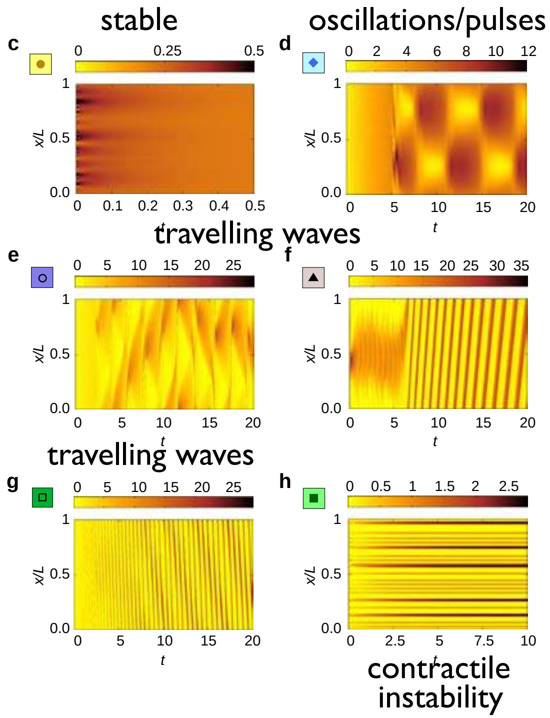
elastic stress   active stress

$$\Gamma \dot{u} = \partial_x \Phi^{'}(\epsilon) + \partial_x \sigma^a(\rho_b)$$

advection   diffusion   turnover

$$\dot{\rho}_b = -\partial_x(\rho_b \dot{u}) + D\partial_x^2 \rho_b + S_m(\epsilon, \rho_b),$$





MyosinII kymographs

Deb Sankar Banerjee, A. Munjal, T. Lecuit and Madan Rao. *Nature Comm*, (2017)18:1121
NATURE COMMUNICATIONS | 8: 1121 | DOI: 10.1038/s41467-017-01130-1 | www.nature.com/naturecommunications

1. Introduction - phenomenology

2. Chemical Instabilities
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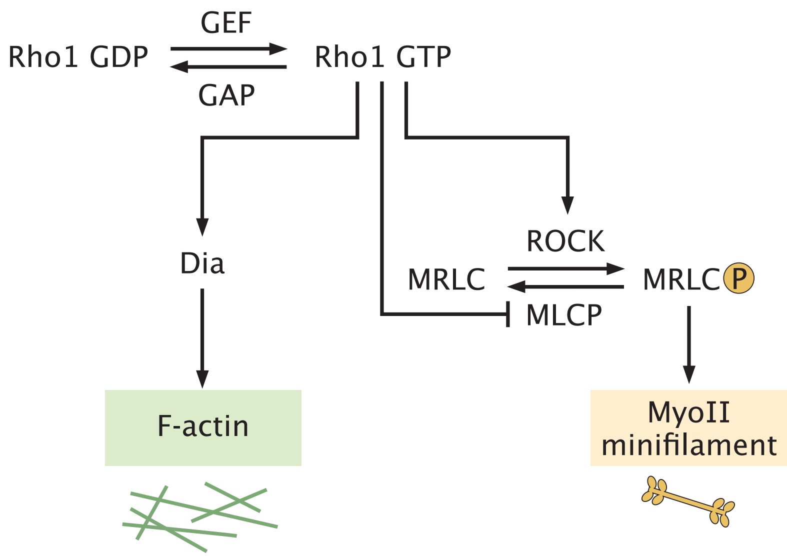
IV - Mechano-chemical Instabilities

- Myosin-II minifilament assembly (processive bipolar motor)

Chemistry

- Rho1 pathway



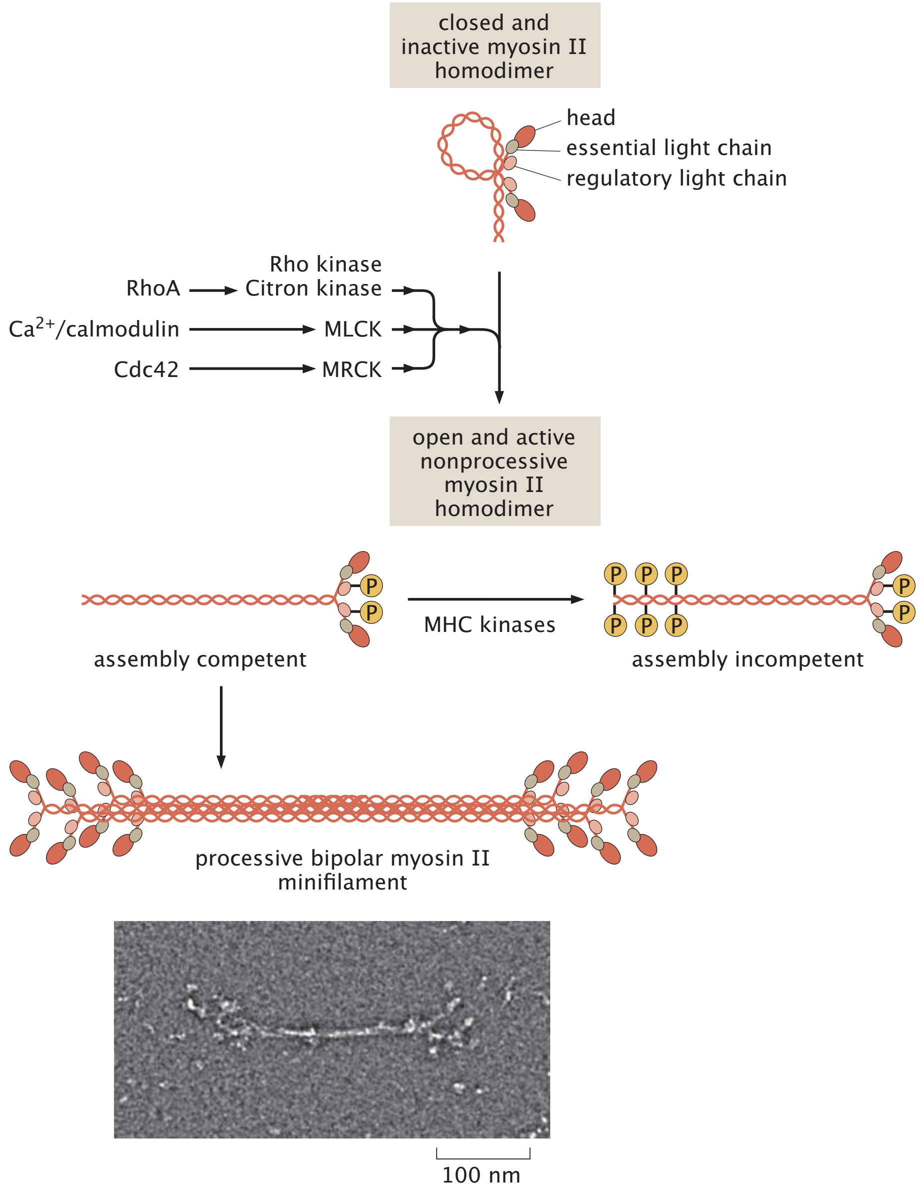
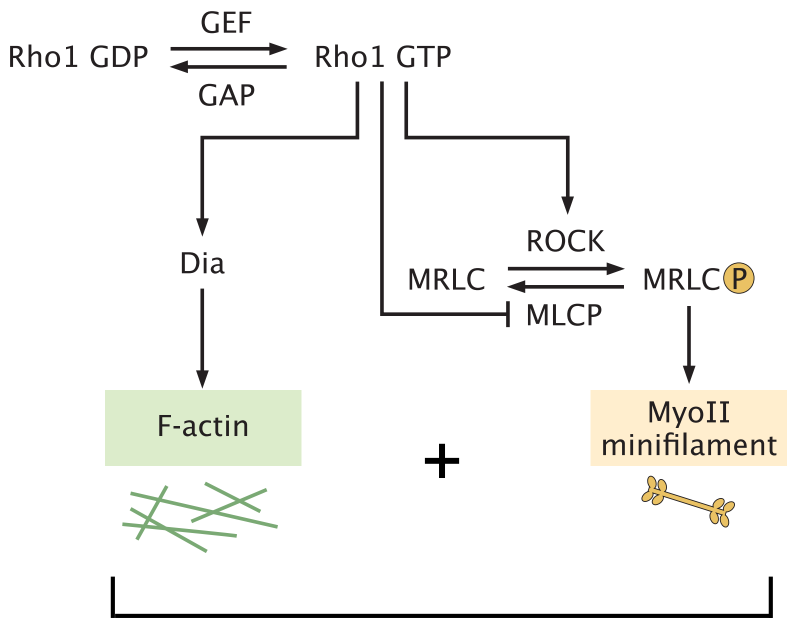


illustration: Nigel Orme.

IV - Mechano-chemical Instabilities

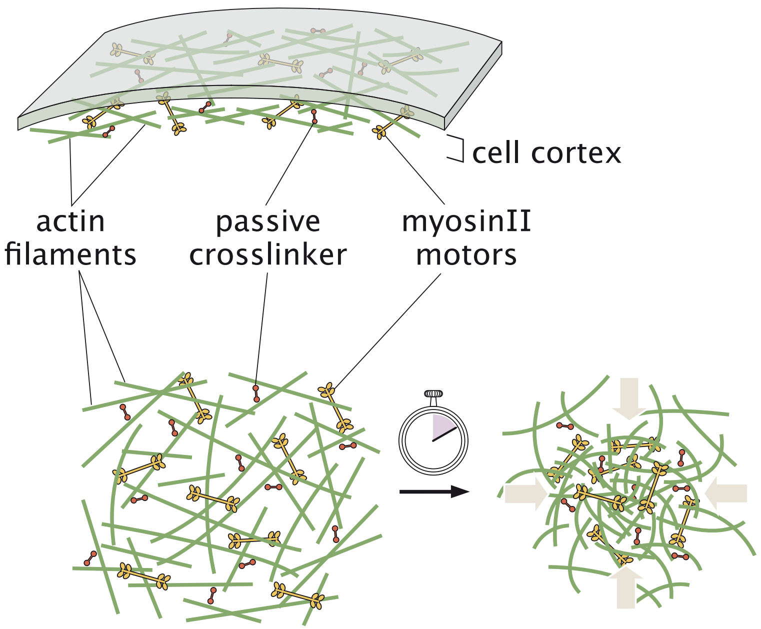
Chemistry

- Rho1 pathway



Mechanics

- Actomyosin contraction



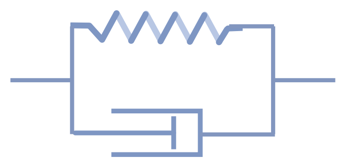
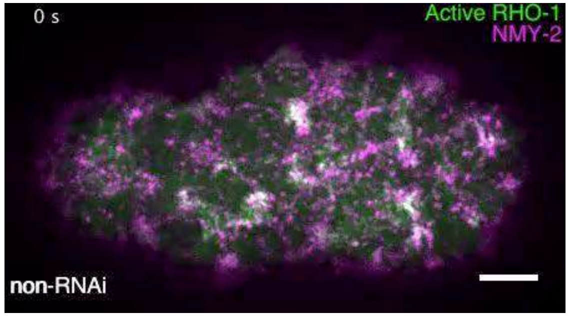


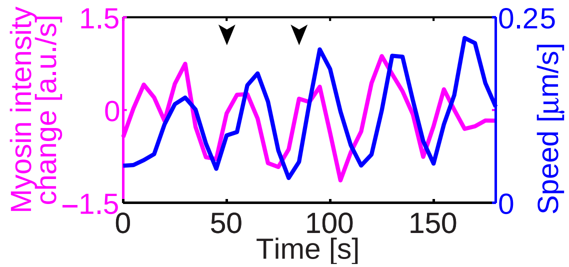
illustration: Nigel Orme.

IV - Mechano-chemical Instabilities

- Pulsatile contraction of actomyosin networks: a mechano-chemical model

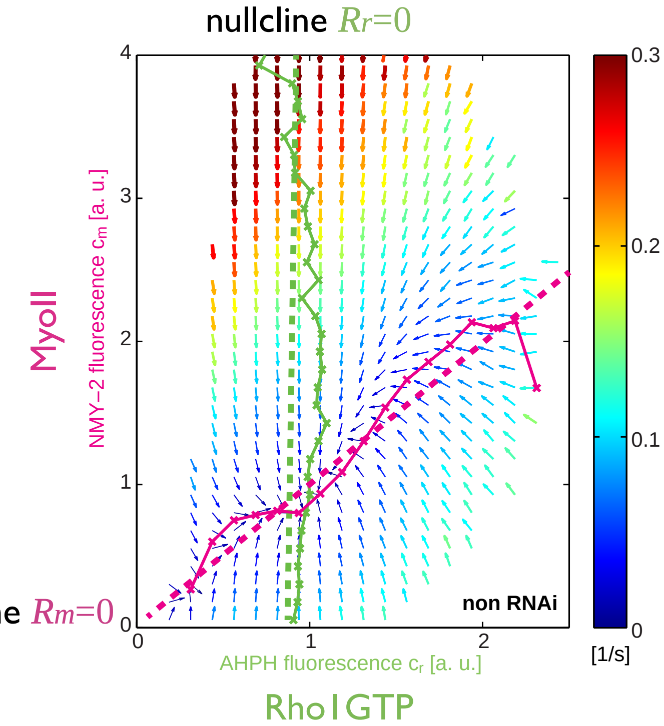
MyoII and Rho1GTP exhibit pulsatile dynamics

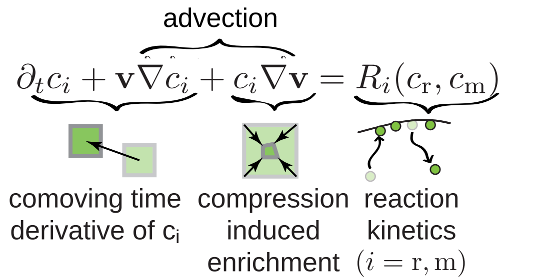




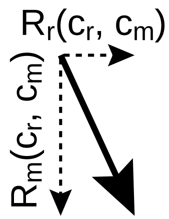
Nullcline analysis:

- Rho1 activation kinetics is independent of MyoII concentration
- MyoII activation kinetics is a function of Rho1 concentration





Calculate Reaction kinetics R_r and R_m (exchange between cytosol and cortex) based on evolution of concentration and flow field



M Nishikawa, SR Naganathan, F Jülicher and S. Grill. *eLife*, (2017) 6:e19595.

IV - Mechano-chemical Instabilities

- Pulsatile contraction of actomyosin networks: a mechano-chemical model

<u>Hydrodynamic mechanochemical Model:</u>

$$\sigma^a = \zeta f(\rho_\mathrm{m})$$
$$\sigma = \eta \partial_x v(x,t) + \sigma^a(\rho_m)$$
$$\partial_x \sigma = \gamma v\,.$$

$$\lambda \partial_x^2 v + \frac{\zeta'}{\lambda}\partial_x f(\rho_\mathrm{m}) - \frac{1}{\lambda} v = 0$$

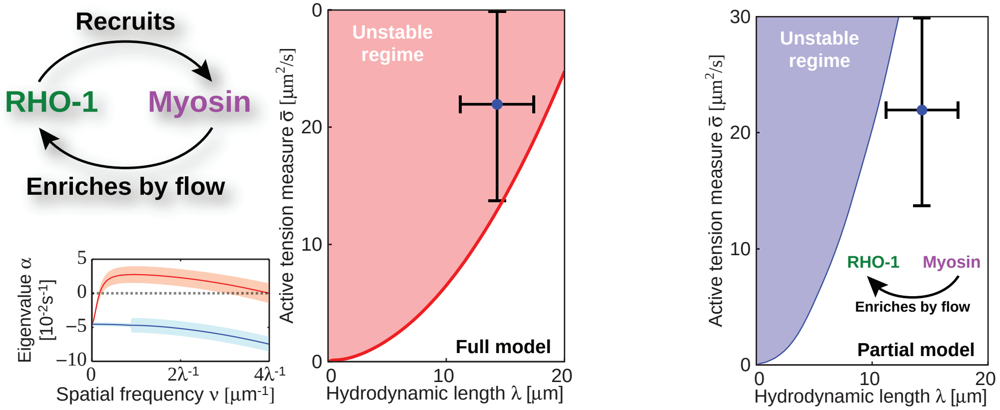
constitutive equation of active gel

$$\zeta' = \frac{\zeta}{\gamma}$$

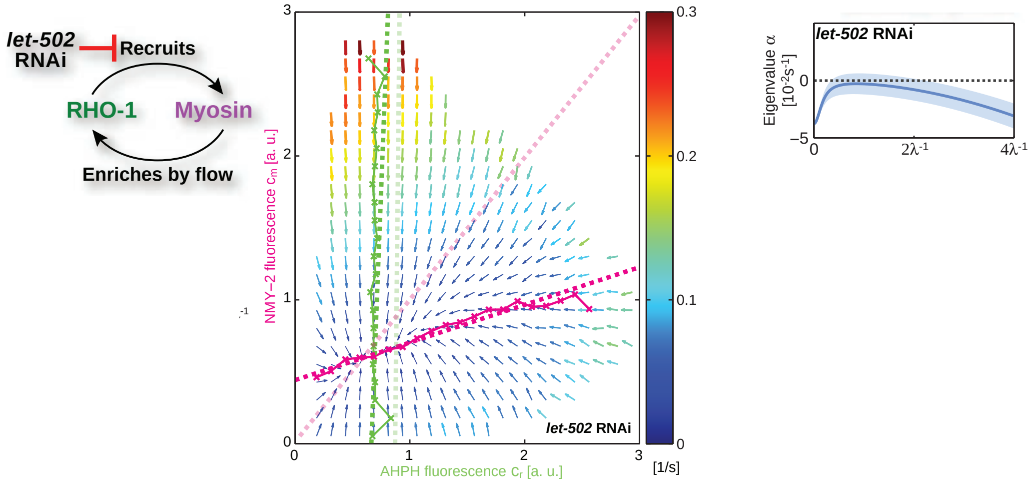
$$\partial_t \rho_i(x,t) + \partial_x j_i(x,t) = R_i(\boldsymbol{\rho}(x,t))$$
$$j_i(x,t) = v(x,t)\rho_i(x,t) - D_i \partial_x \rho_i(x,t)\,,$$

conservation law: reaction kinetics and advection

Linear stability analysis reveals that instability requires large enough active stress and explains instability of *C. elegans* cortex



Instability requires Rho1 dependent activation of MyosinII



YET: Pulsations do not emerge from the model

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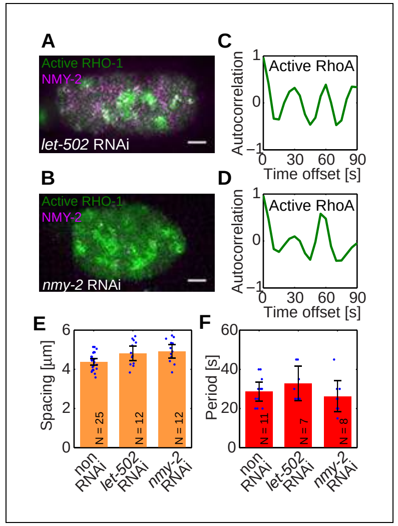
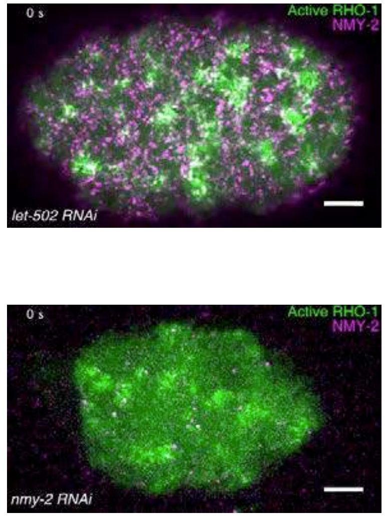
M Nishikawa, SR Naganathan, F Jülicher and S. Grill. *eLife*, (2017) 6:e19595.

IV - Mechano-chemical Instabilities

- Pulsatile contraction of actomyosin networks: a mechano-chemical model

Rho1GTP pulsations persists following inhibition of MyosinII



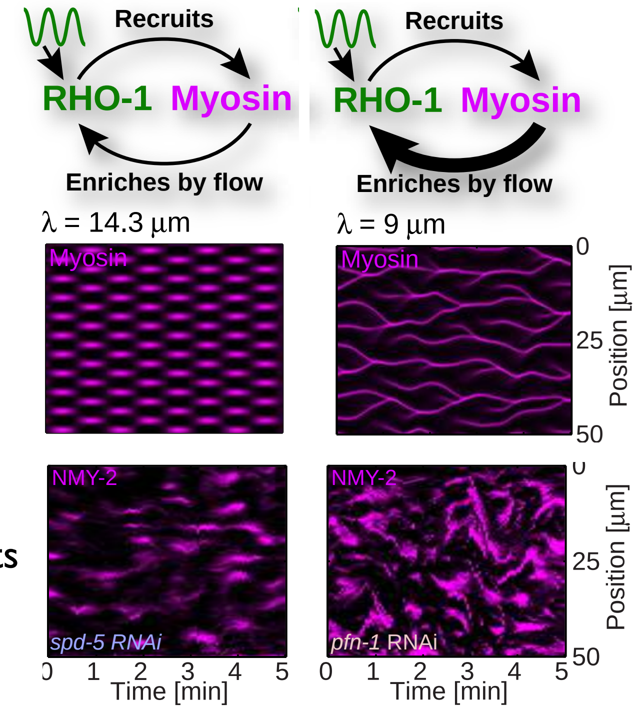


Pulsatile Rho1 signalling can entrain pulsatile contractility

Increasing the mechanical feedback (eg. increase advective flow speed via reduction of hydrodynamic length) causes more irregular instabilities

Simulations

Experiments

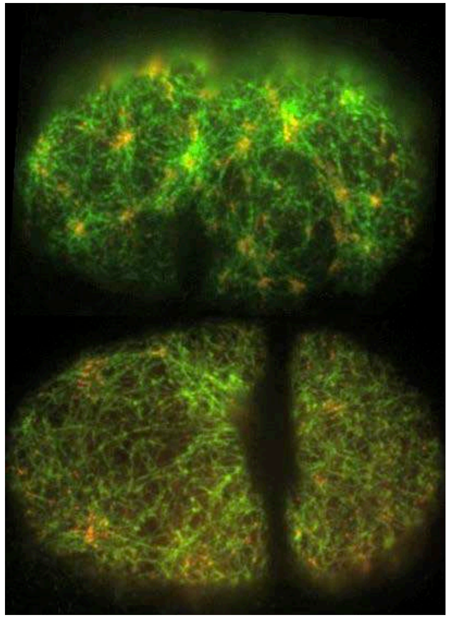


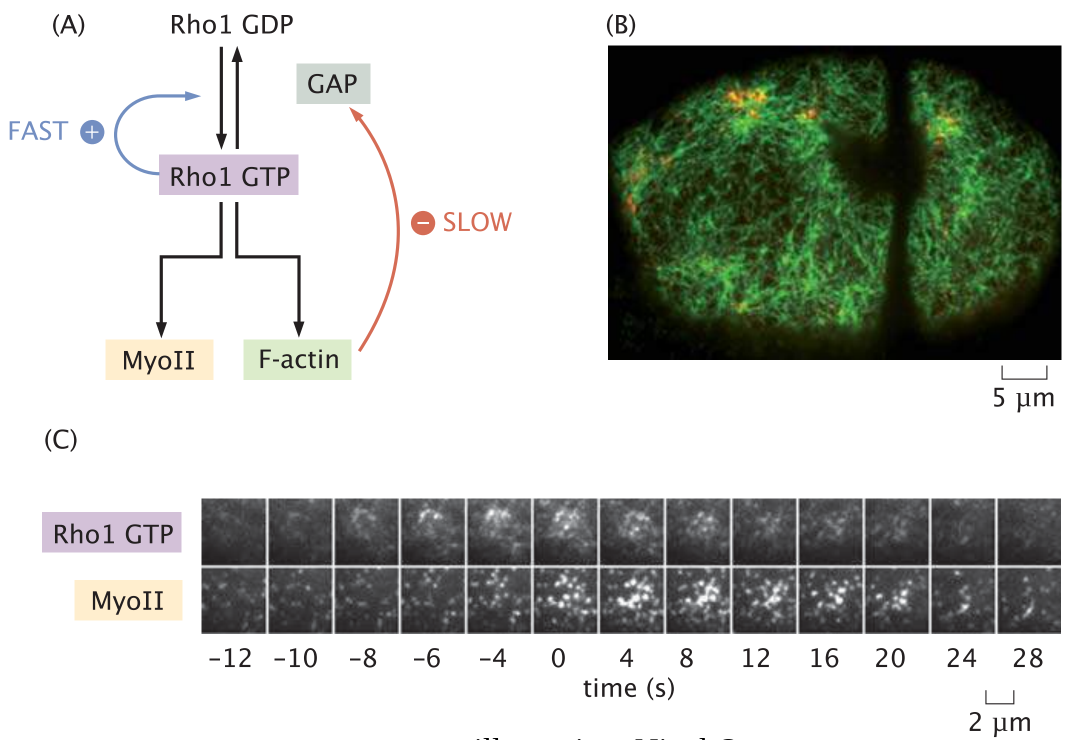
M Nishikawa, SR Naganathan, F Jülicher and S. Grill. *eLife*, (2017) 6:e19595.

IV - Mechano-chemical Instabilities

- Pulsatile contraction of actomyosin networks: a mechano-chemical model

Origin of Rho1GTP oscillations.





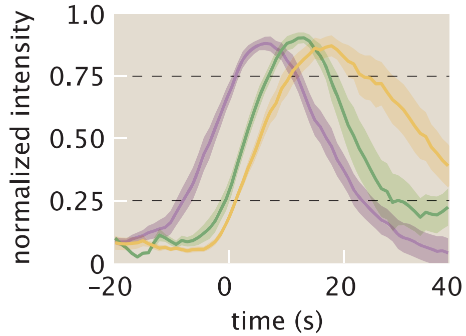


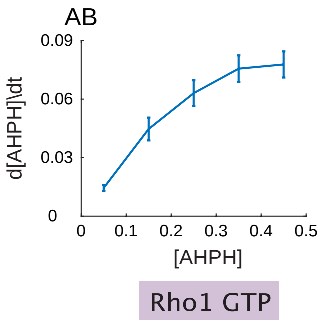
illustration: Nigel Orme.

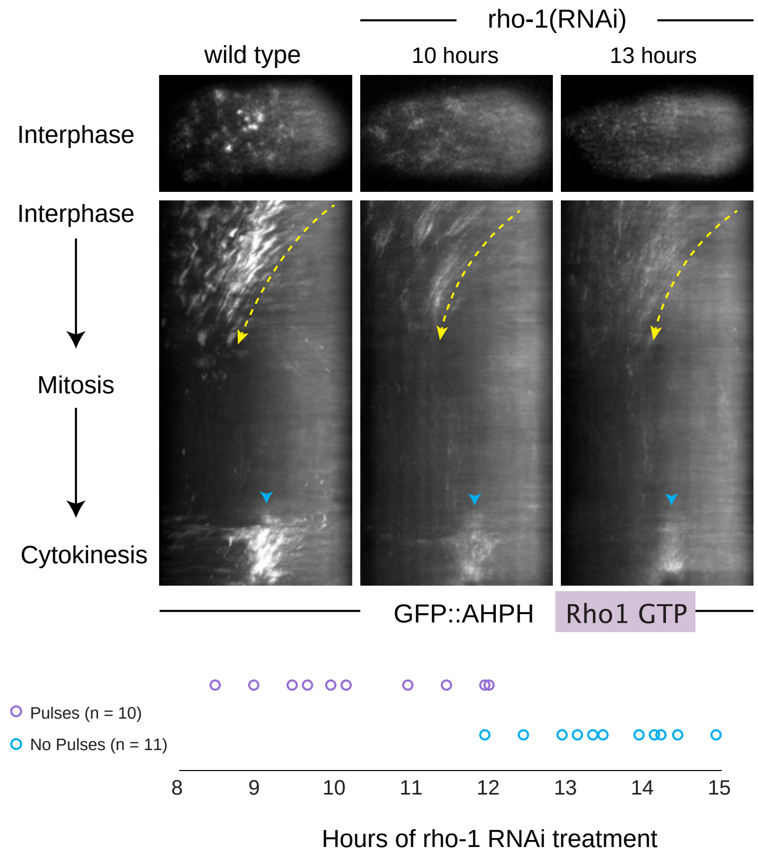
François Robin, J.B Michaux, W. McFadden and Edwin Munro. *J Cell Biol. 2018 Oct 1. doi: 10.1083/jcb.201806161.*

IV - Mechano-chemical Instabilities

- Pulsatile contraction of actomyosin networks: a mechano-chemical model

Characteristics of an Excitable Chemical system:
- Rho1 positive Feedback and Existence of threshold



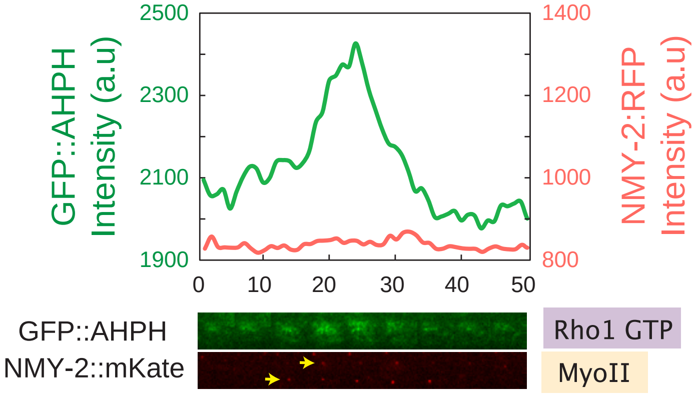


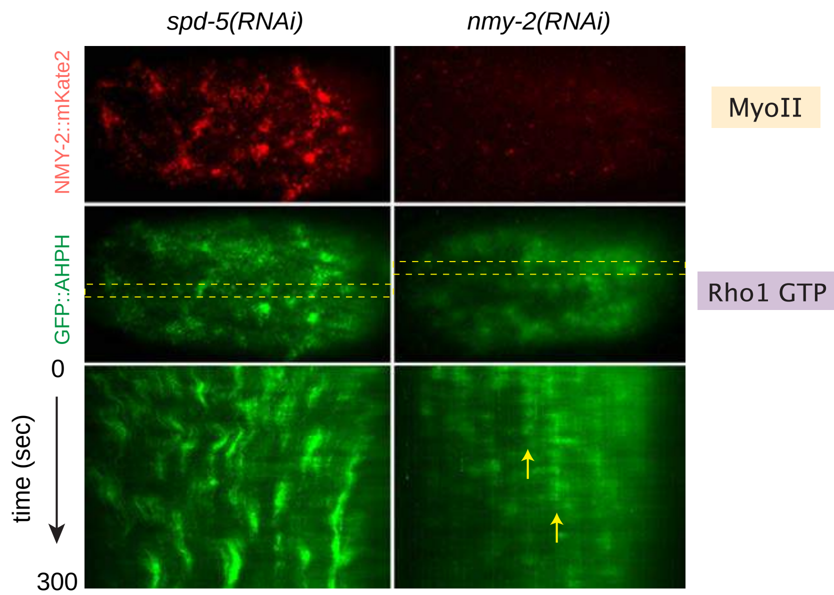
François Robin, J.B Michaux, W. McFadden and Edwin Munro. *J Cell Biol. 2018 Oct 1. doi: 10.1083/jcb.201806161.*

IV - Mechano-chemical Instabilities

- Pulsatile contraction of actomyosin networks: a mechano-chemical model

Rho1 positive Feedback is *Independent* of MyoII activation



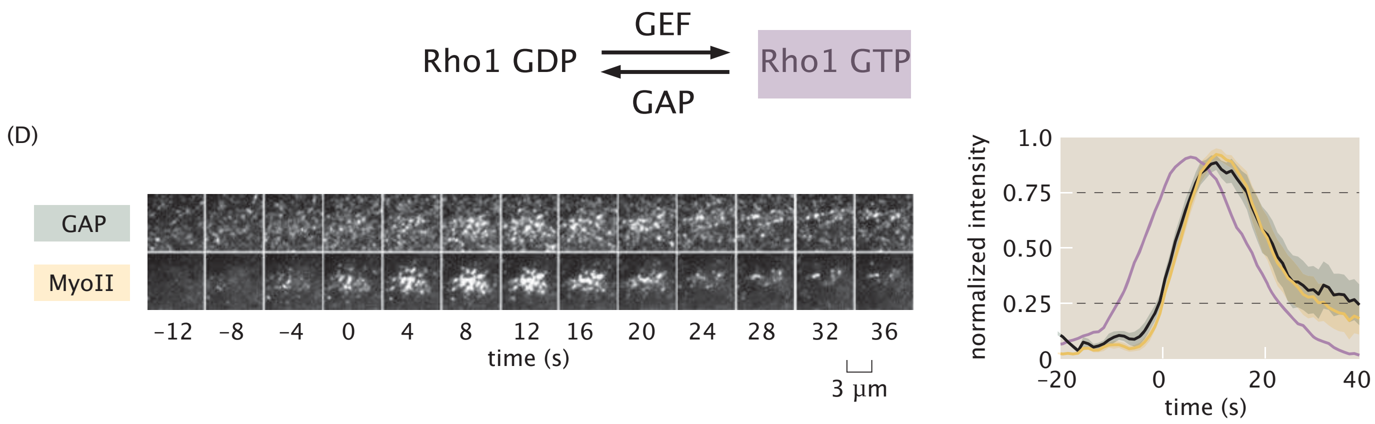


François Robin, J.B Michaux, W. McFadden and Edwin Munro. *J Cell Biol. 2018 Oct 1. doi: 10.1083/jcb.201806161.*

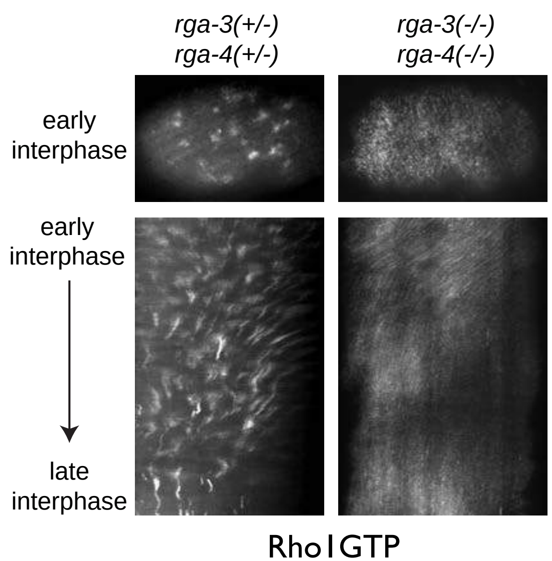
IV - Mechano-chemical Instabilities

- Pulsatile contraction of actomyosin networks: a mechano-chemical model

Delayed Negative Feedback depends on recruitment of Rho1GAP



- Pulses of a RhoGAP are synchronous with MyoII pulses
- Rapid accumulation of GAP coincides with reduction and reversal in Rho1GTP concentration
- RhoGAPs (RGA) are required for pulses of Rho1GTP

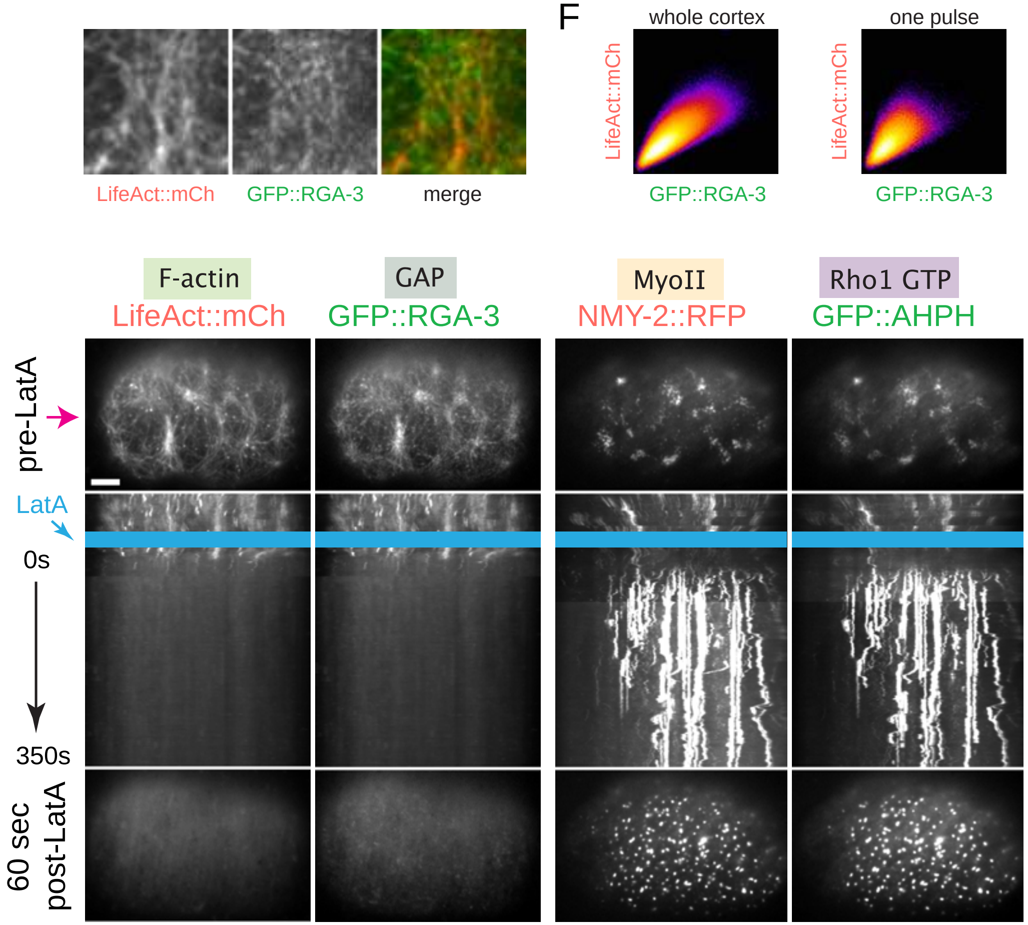


François Robin, J.B Michaux, W. McFadden and Edwin Munro.
J Cell Biol. 2018 Oct 1. doi: 10.1083/jcb.201806161.

IV - Mechano-chemical Instabilities

- Pulsatile contraction of actomyosin networks: a mechano-chemical model

  Rho1GAP decorates actin filaments and is recruited to the cell cortex by actin filaments

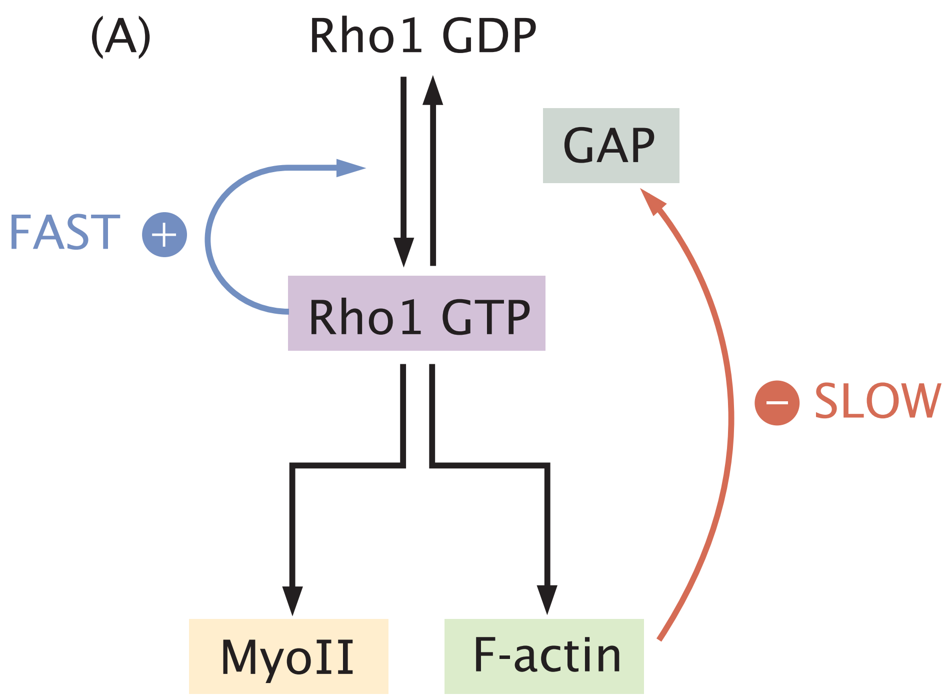


François Robin, J.B Michaux, W. McFadden and Edwin Munro. *J Cell Biol. 2018 Oct 1. doi: 10.1083/jcb.201806161.*

IV - Mechano-chemical Instabilities

- Pulsatile contraction of actomyosin networks: a mechano-chemical model

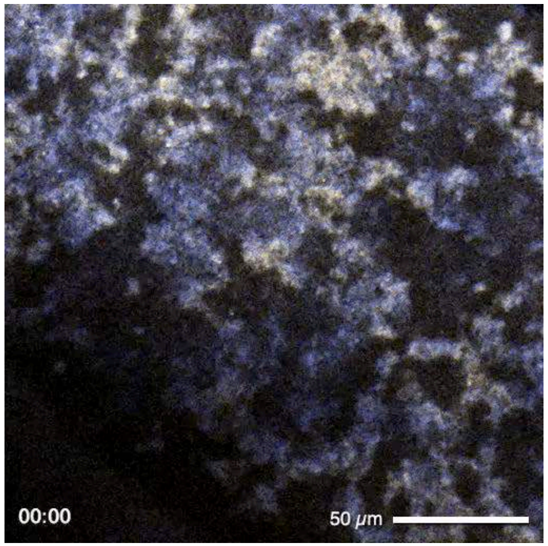
Actomyosin oscillations emerge from autocatalytic activation of Rho1 and delayed negative feedback inhibition



IV - Mechano-chemical Instabilities

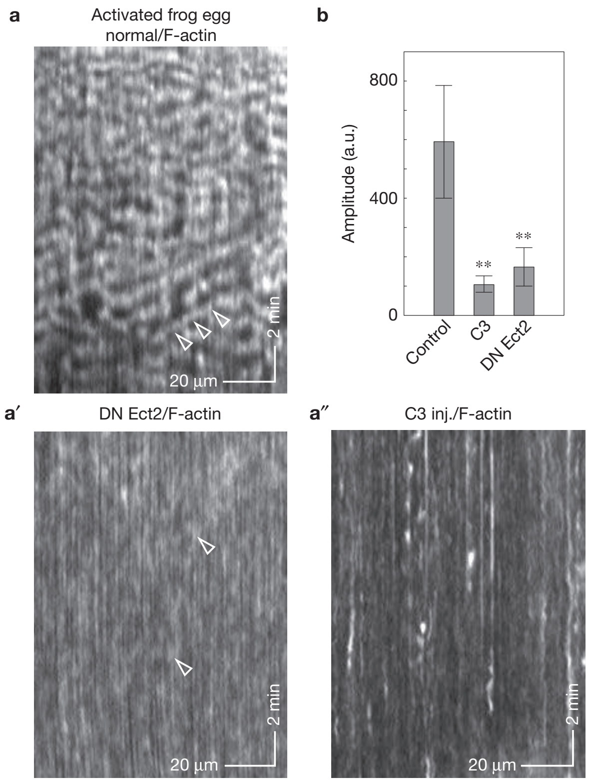
- Travelling waves in actomyosin networks: a mechano-chemical model

$\sim 0.225\ \mu m\ s^{-1}$

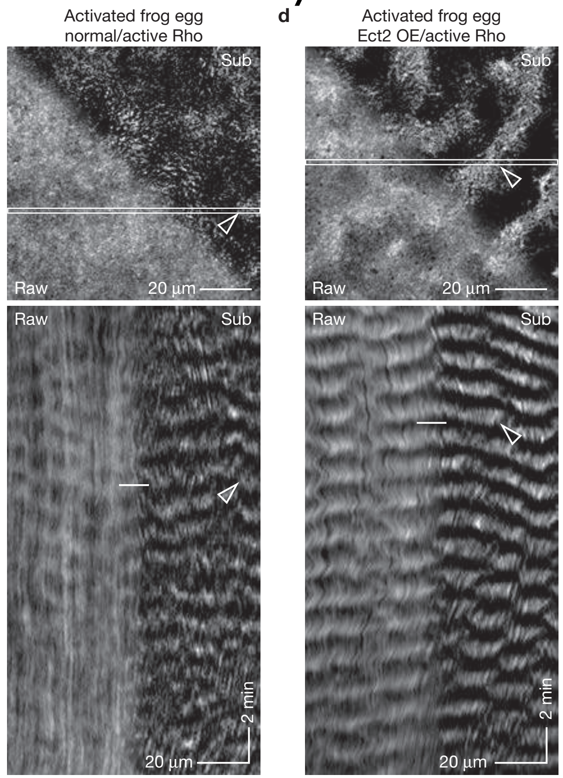


LifeAct : rapid binding — wave front
Utrophin: slow binding — wave back

- Rho1 is required for Actin waves



- Rho1 waves amplitude increased by RhoGEF



Ect2/Rho1GEF

GEF

Rho1 GDP ⇌ Rho1 GTP*

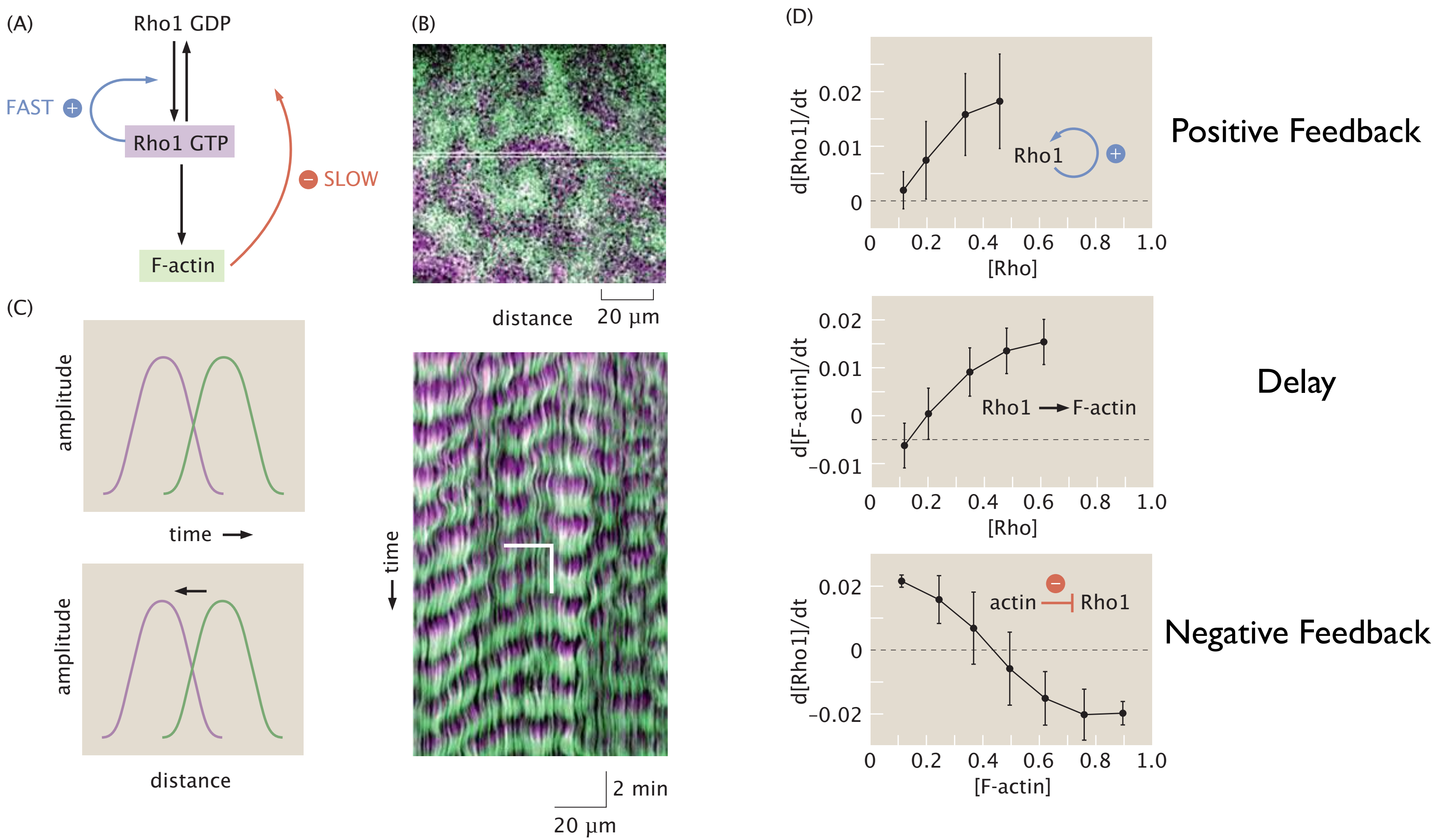
GAP

William Bement et al and George von Dassow. *Nature Cell Biology* 17(11):1471-83 (2015)

IV - Mechano-chemical Instabilities

- Travelling waves in actomyosin networks: a mechano-chemical model

  - Characteristics of an Excitable system:

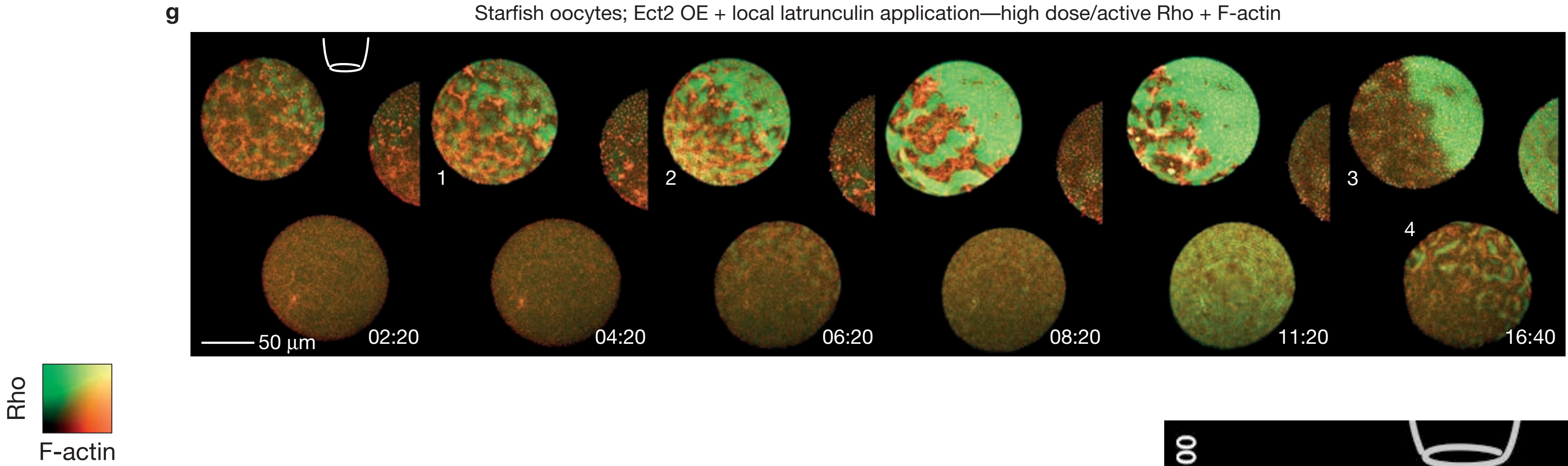


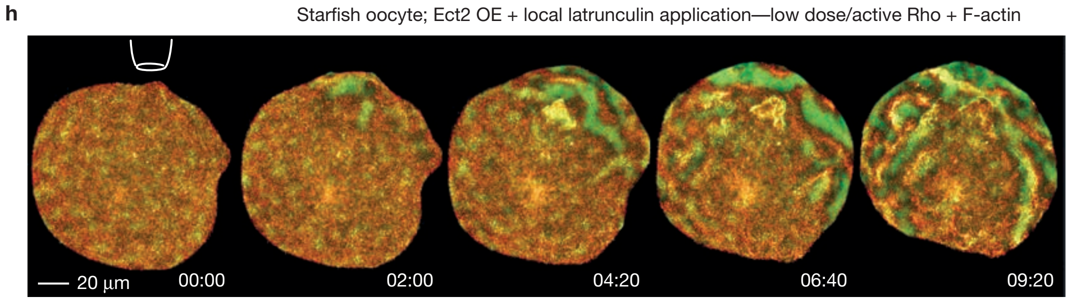
William Bement et al and George von Dassow. *Nature Cell Biology* 17(11):1471-83 (2015)
illustration: Nigel Orme.

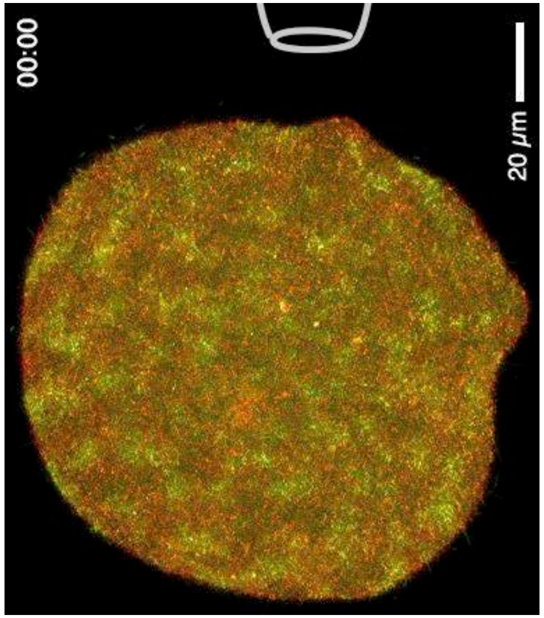
IV - Mechano-chemical Instabilities

- Travelling waves in actomyosin networks: a mechano-chemical model

Actin depolymerisation increases Rho1 amplitude and wave length







William Bement et al and George von Dassow. *Nature Cell Biology* 17(11):1471-83 (2015)

IV - Mechano-chemical Instabilities

- Excitable dynamics of actomyosin networks: a mechano-chemical model

Actomyosin oscillations emerge from autocatalytic activation of Rho1 and delayed negative feedback inhibition

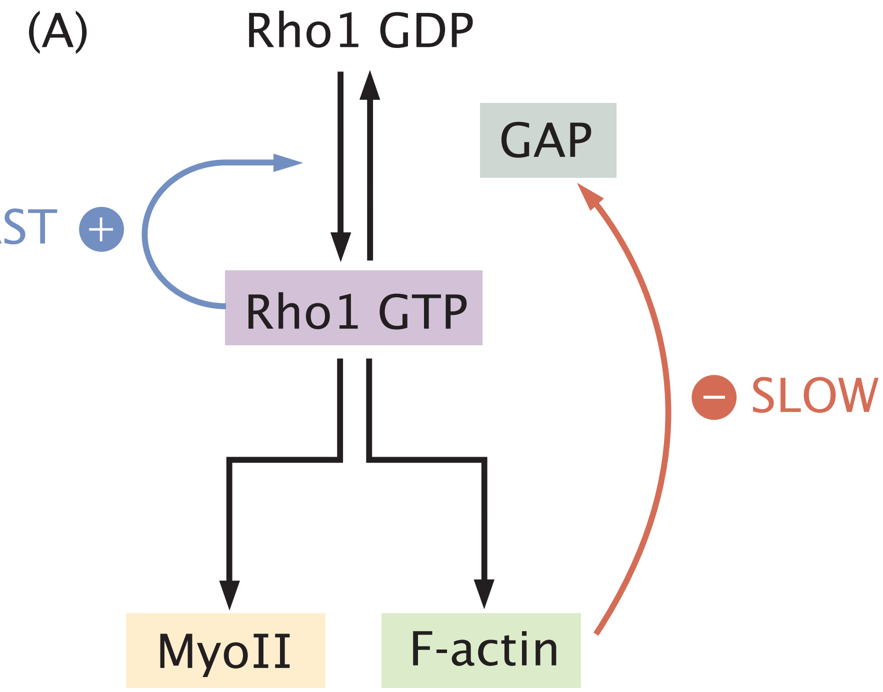


illustration: Nigel Orme.

IV - Mechano-chemical Instabilities

- Biochemical excitability of actomyosin networks
- Mechanical feedbacks:

Mechanical Feedbacks:

- Tension dependent MyosinII unbinding kinetics (strain dependent stabilisation)

  Y. Ren et al D. Robinson *Curr. Biol.* 19:1421 2009 (via actin cross linker Cortexilin)
  Effler et al D. Robinson *Curr. Biol.* 16:1962 2006
  Luo et al D. Robinson *Biophy. J.* 102:238 2012

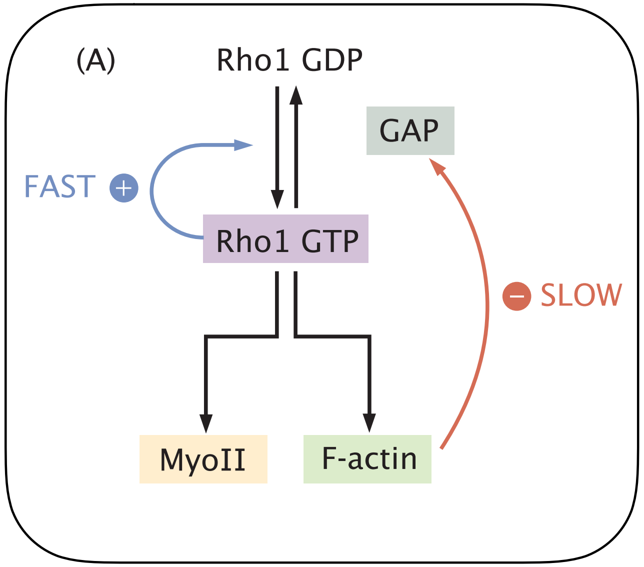
- Tension-dependent filament assembly/disassembly

  K. Hayakawa et al, M. Sokabe. *JCB* 195:721 2011 (tension suppresses Cofilin binding)

- Tension dependent activation of MyoII

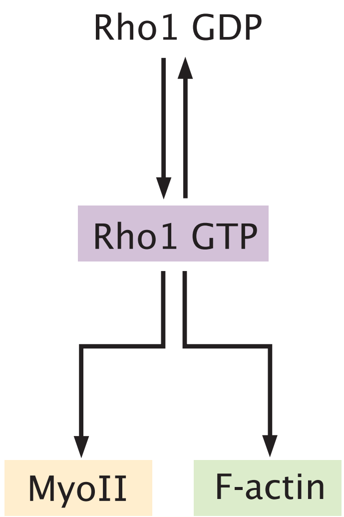
- Advection driven concentration of upstream activators

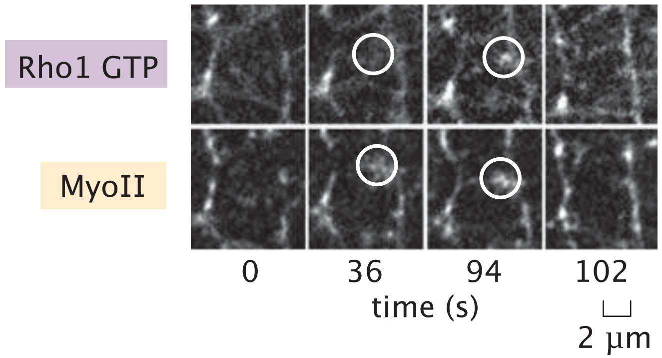
  K. Vijay Kumar, J. Bois, Frank Jülicher and Stephan Grill. *PRL.* (2014). 112, 208101
  Munjal, A., Philippe, J.-M., Munro, E. & Lecuit, T. *Nature* 524, 351–355 (2015).
  M. Nishikawa, SR Naganathan, F. Jülicher and S. Grill. e*Life* 2017;6:e19595. DOI: 10.7554/eLife.19595

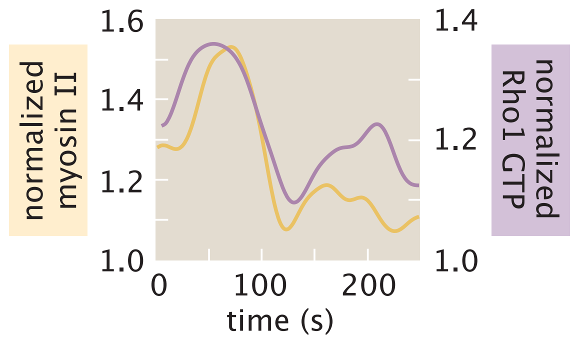


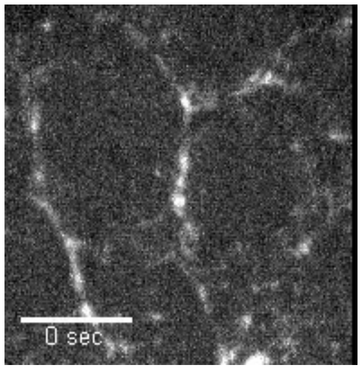
- Mechanical feedback in excitable actomyosin networks

Pulsation of Myosin-II and its activators Rho1GTP, ROK

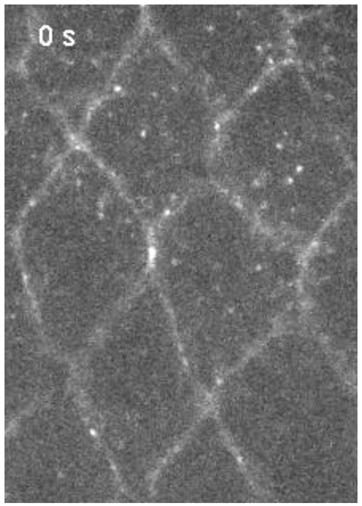








MyoII::GFP



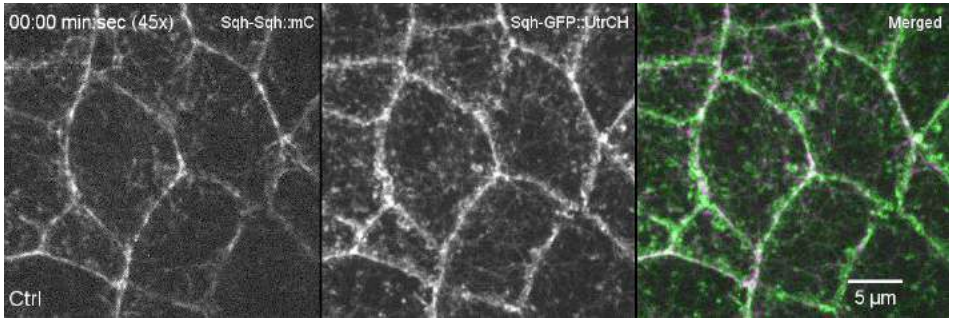
Rho1GTP::GFP

Munjal, A., Philippe, J.-M., Munro, E. & Lecuit, T. *Nature* 524, 351–355 (2015).
illustration: Nigel Orme.

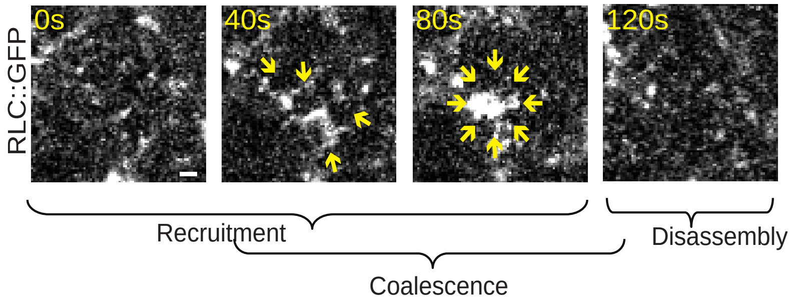
IV - Mechano-chemical Instabilities

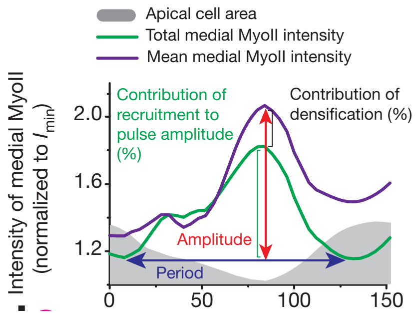
- Mechanical feedback in excitable actomyosin networks

MyoII::mCherry F-actin (UtrophinABD::GFP)

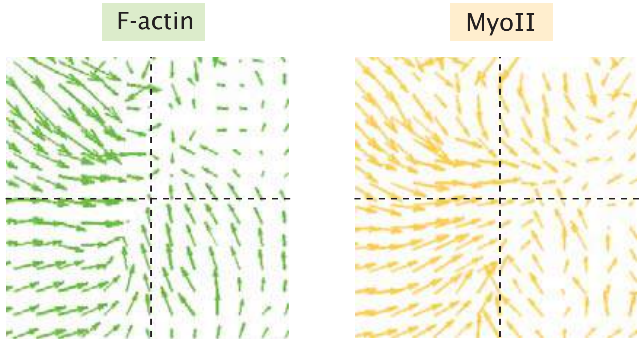


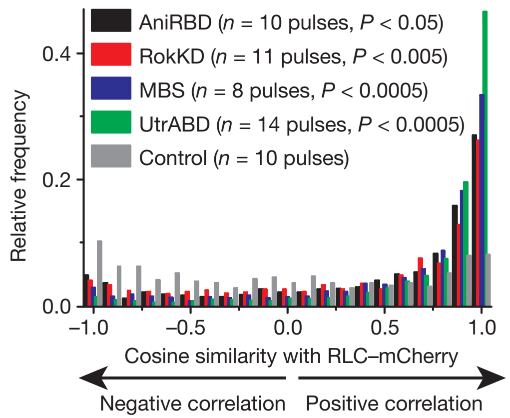
Non-linear amplification of MyosinII recruitment during pulse assembly





Advection of all biochemical network components



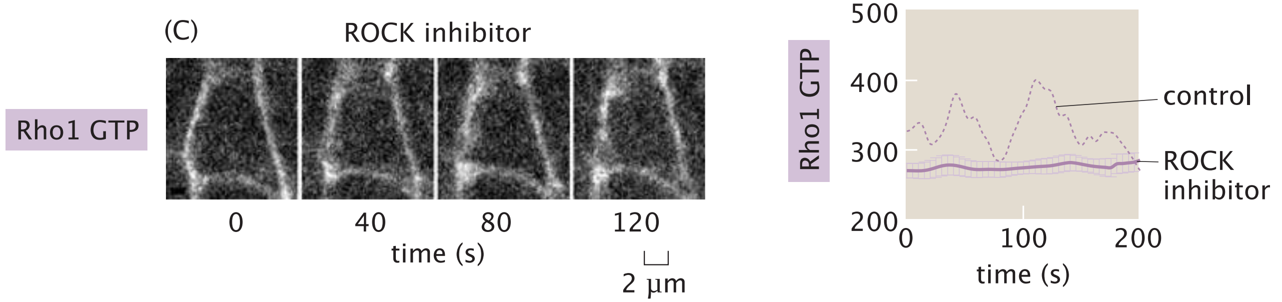


Munjal, A., Philippe, J.-M., Munro, E. & Lecuit, T. *Nature* 524, 351–355 (2015).
illustration: Nigel Orme.

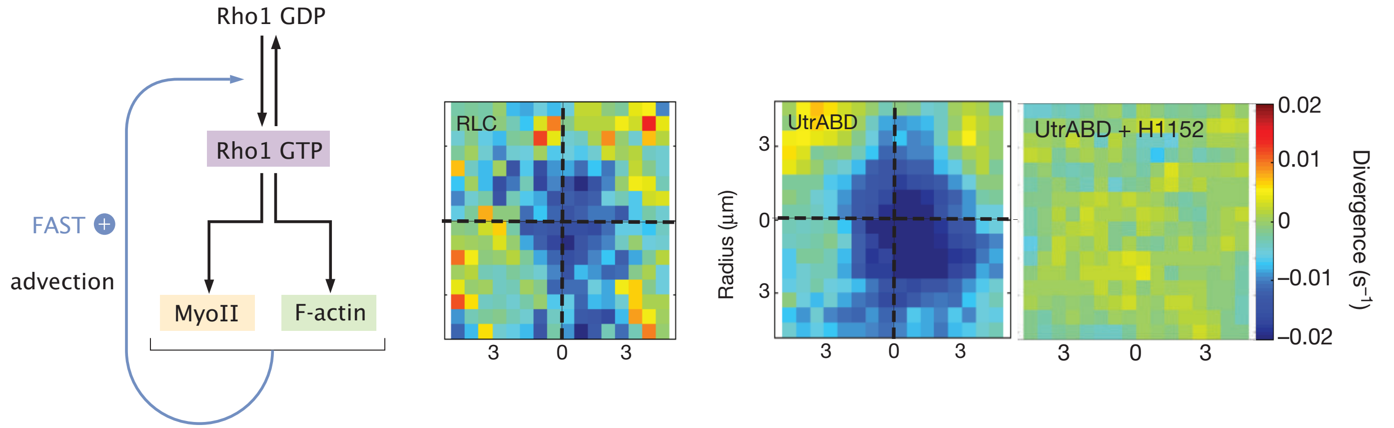
IV - Mechano-chemical Instabilities

- Mechanical feedback in excitable actomyosin networks

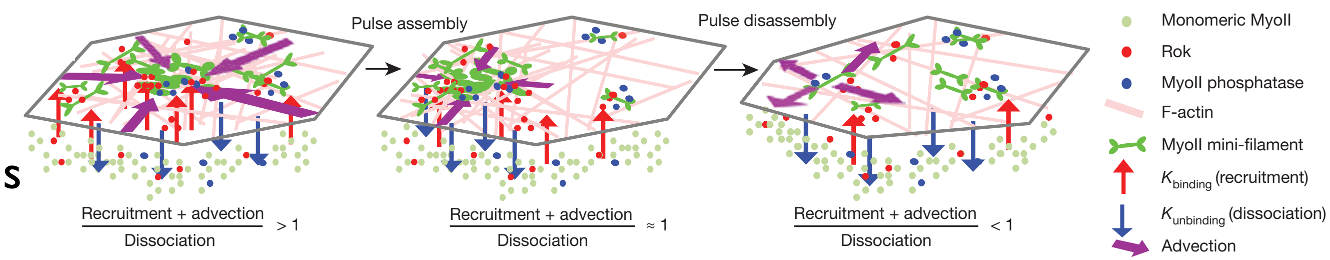
Pulsation of Rho1GTP requires MyosinII activation



All network components show convergent advection during pulse assembly
Advection requires MyoII



Competition between motor driven advection and turnover underlies oscillations



Munjal, A., Philippe, J.-M., Munro, E. & Lecuit, T. *Nature* 524, 351–355 (2015).
illustration: Nigel Orme.

1. Introduction - phenomenology

2. Chemical Instabilities
   21. Spatial instabilities - Turing patterns
   22. Temporal instabilities - Excitability
   23. Spatial-temporal instabilities: waves

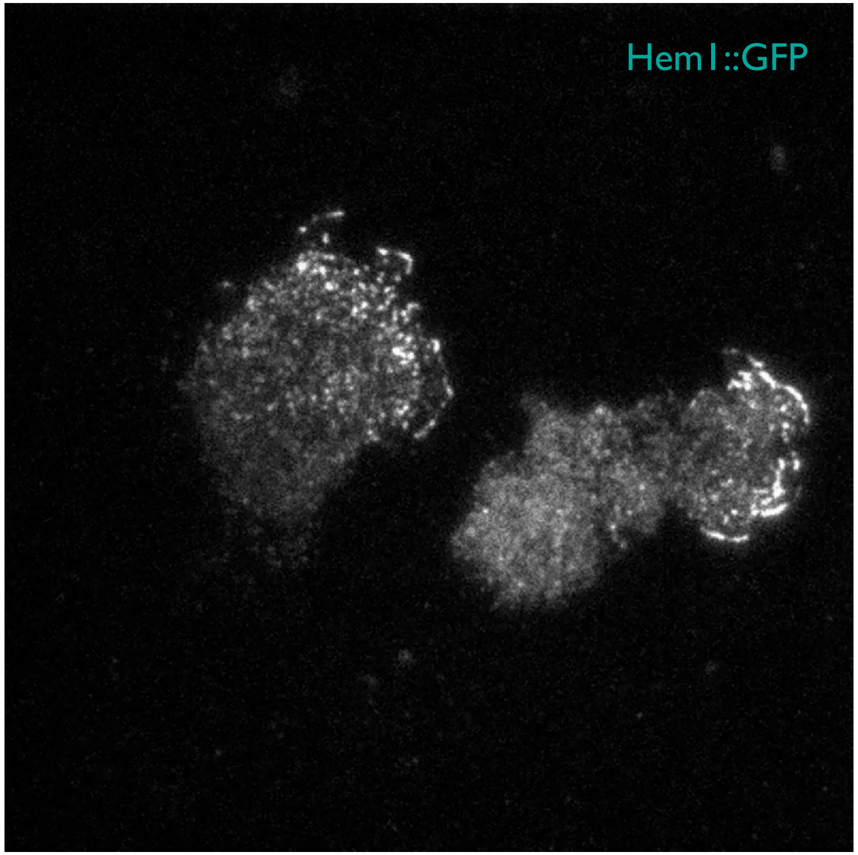
3. Mechanical instabilities
   31. Cellular aggregates: viscoelastic model
   32. Active gel: hydrodynamic and viscoelastic models

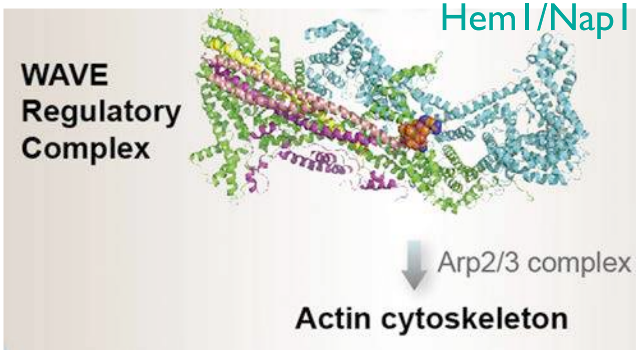
4. Mechano-chemical Instabilities
   41. Mechano-chemical coupling: actomyosin dynamics
   42. Actin based trigger waves

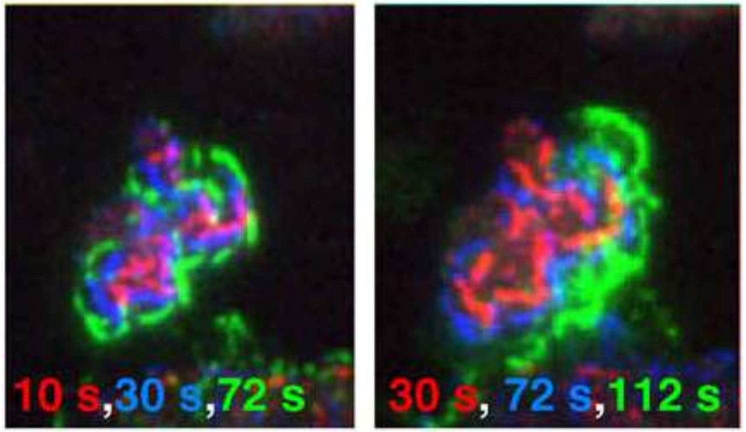
5. Developmental significance: impact on cellular and tissue morphogenesis

III - Mechano-chemical Instabilities

- An actin based wave generator during cell motility

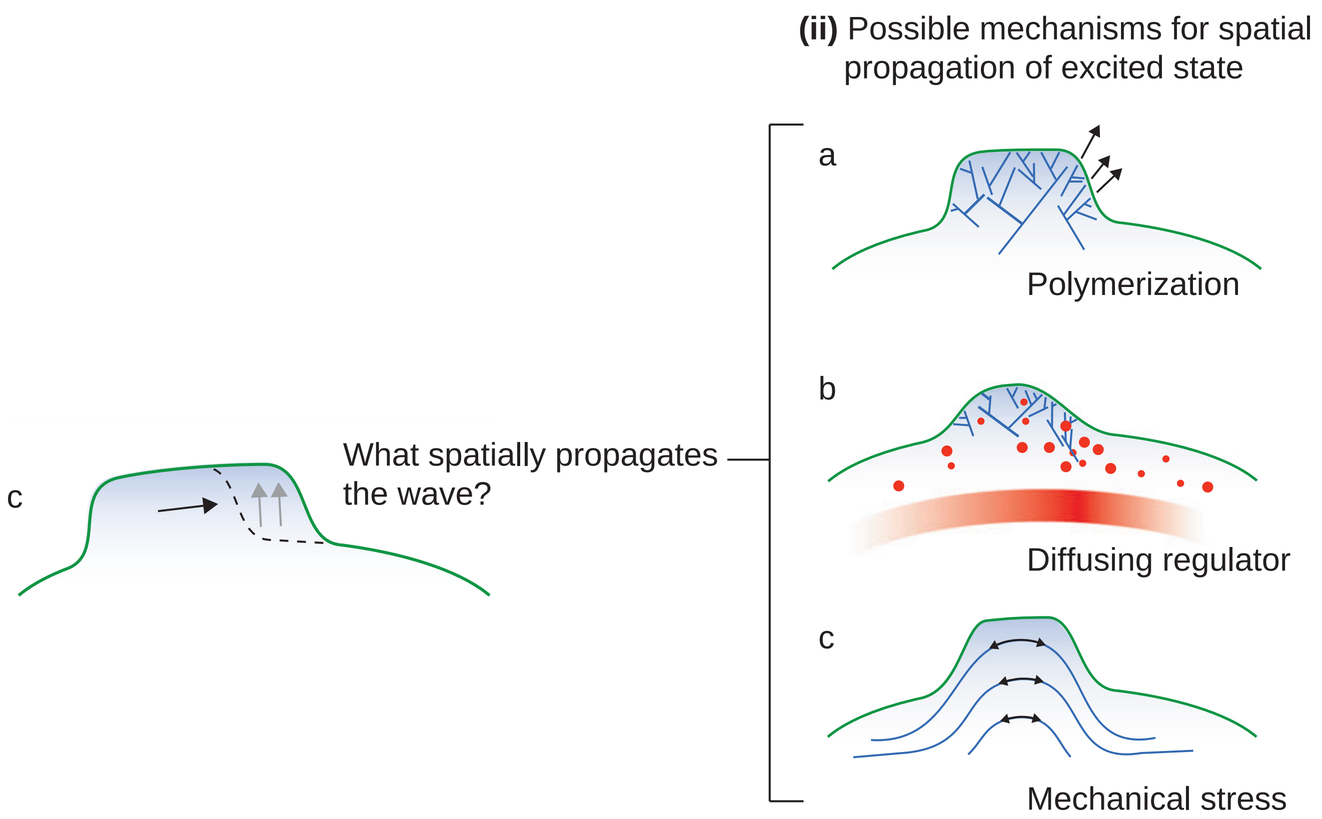






Orion Weiner, et al., and Mark Krischner *PLoS Biol* 5(9): e221. doi:10.1371/ journal.pbio.0050221

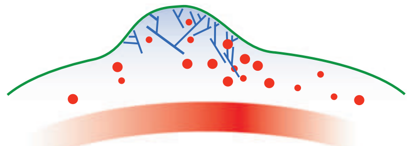
Mechano-chemical propagation of trigger waves



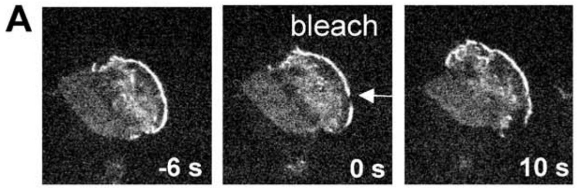
Jun Allard and Alex Mogilner. *Current Opinion in Cell Biology* 2013, 25:107-115.

III - Mechano-chemical Instabilities

- An actin based wave generator during cell motility



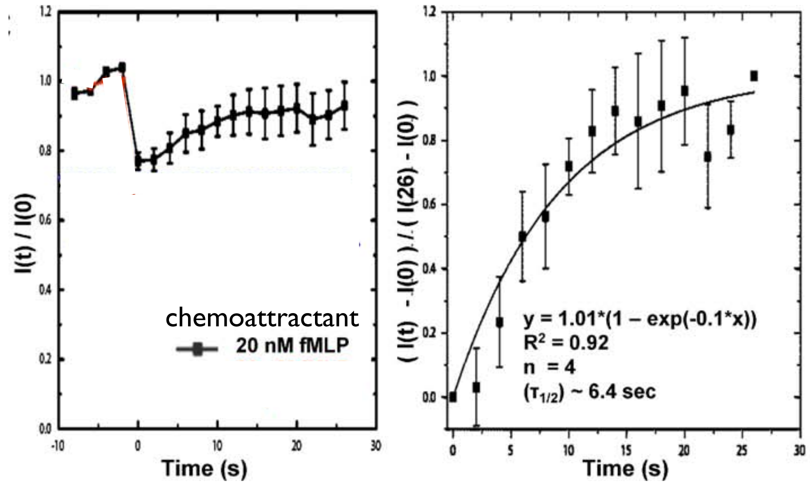
Hem1-YFP

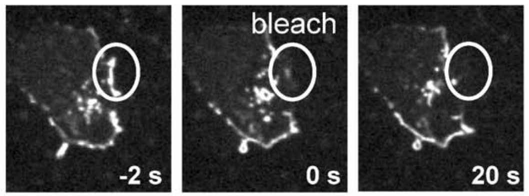


- The Wave2 complex dynamically equilibrates within a few seconds between the cytosol and the membrane

- The movement of the Wave2 front is not due to the translocation of the protein but to its dynamics recruitment in a wave-like manner

Hem1-YFP



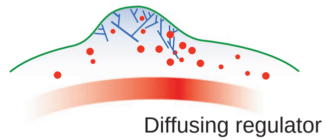


+Latrunculin A

- Rapid equilibration requires actin filaments

Orion Weiner, et al., and Mark Krischner *PLoS Biol* 5(9): e221. doi:10.1371/ journal.pbio.0050221

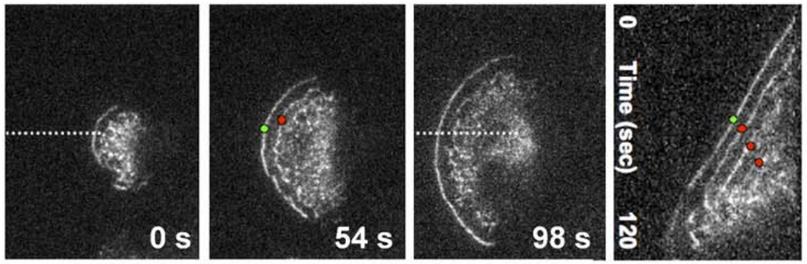
III - Mechano-chemical Instabilities



- The Hem1 wave has characteristics of a trigger wave

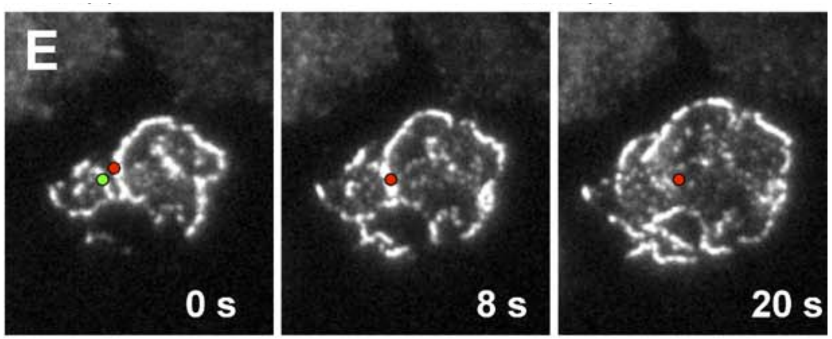
- Successive trigger waves at the cell edge with refractory period

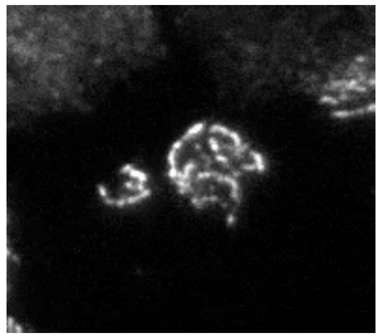
Hem1-YFP

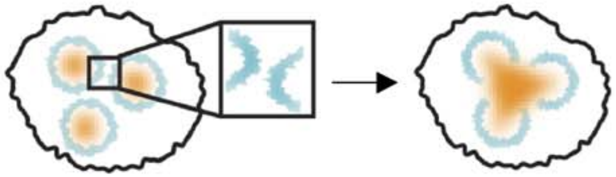


- Colliding waves annihilate

(key property of trigger wave, reflecting refractory period)

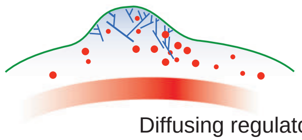




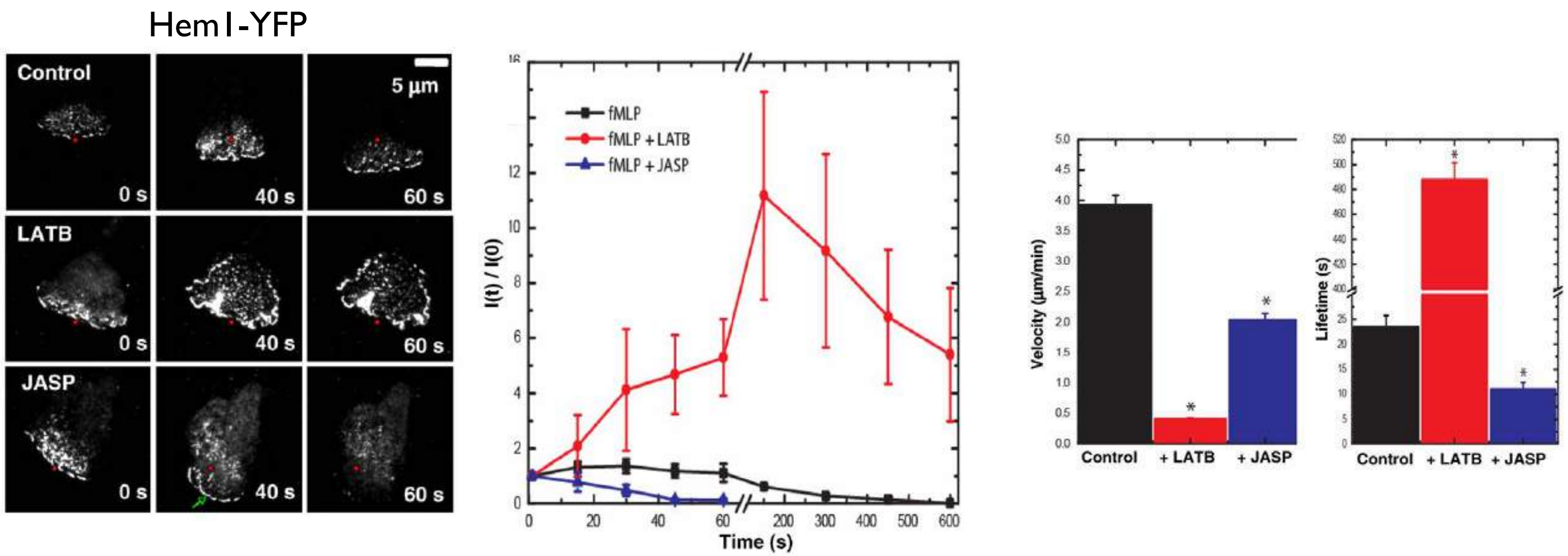


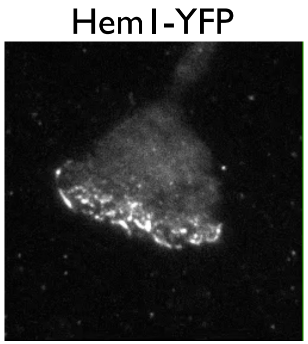
Orion Weiner, et al., and Mark Krischner *PLoS Biol* 5(9): e221. doi:10.1371/ journal.pbio.0050221

III - Mechano-chemical Instabilities

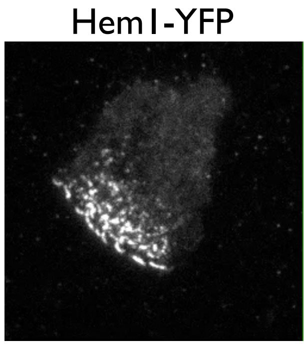


- Actin filaments provide inhibitory signal on Wave2 trigger wave dynamics.





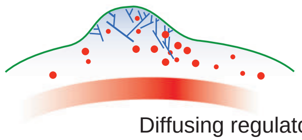
Actin destabilisation (LatA)



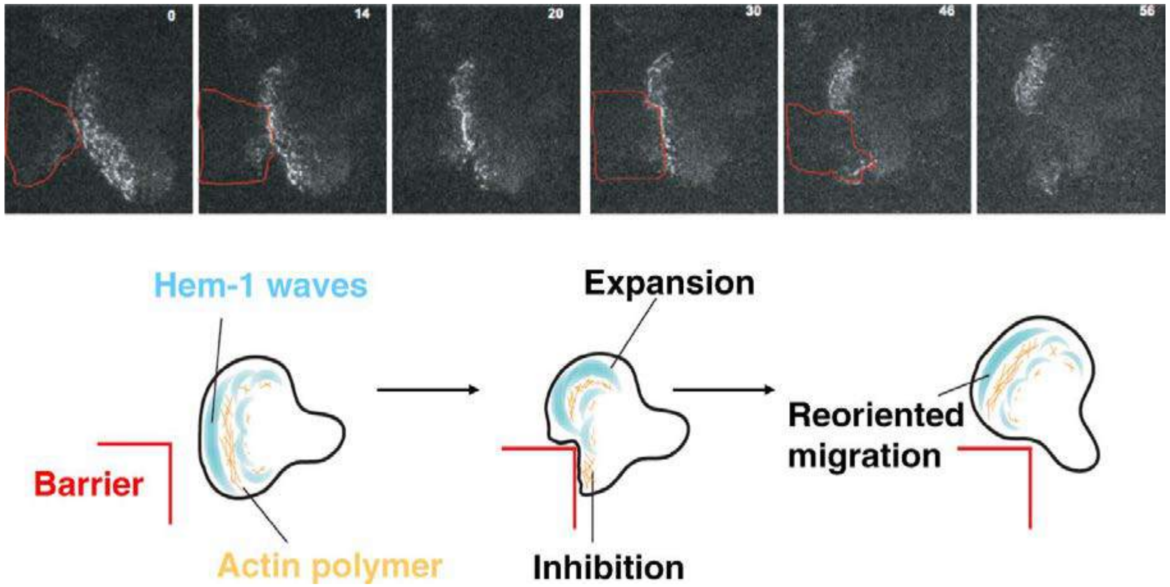
Actin stabilisation (Jasp)

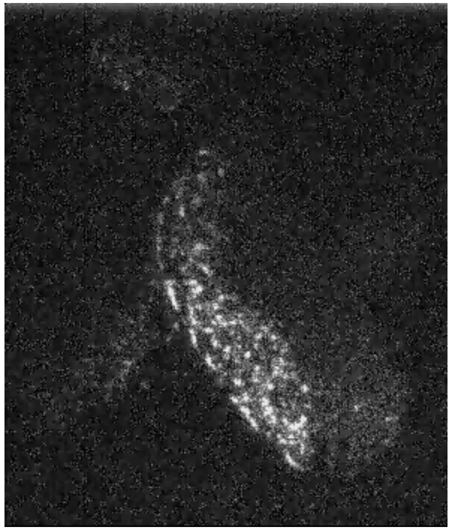
Orion Weiner, et al., and Mark Krischner *PLoS Biol* 5(9): e221. doi:10.1371/ journal.pbio.0050221

III - Mechano-chemical Instabilities



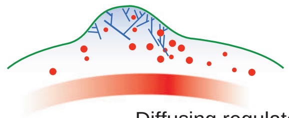
- Blocking membrane protrusion by mechanical barrier leads to wave collapse
- Induction of new wave in adjacent cell region
- Adaptative strategy for cell motility



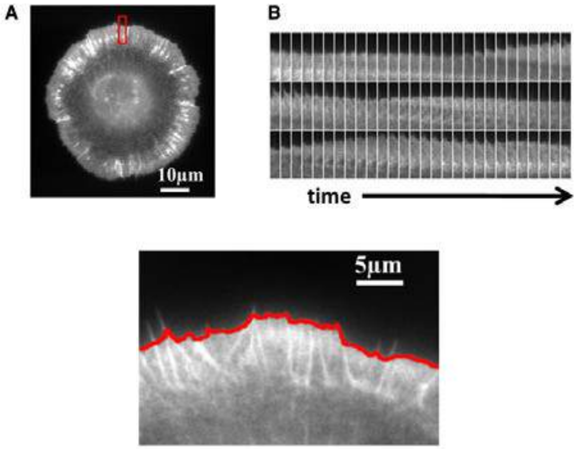


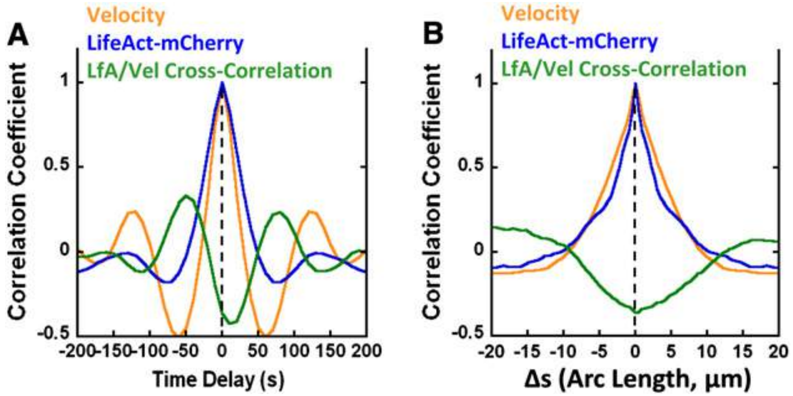
Orion Weiner, et al., and Mark Krischner *PLoS Biol* 5(9): e221. doi:10.1371/ journal.pbio.0050221

III - Mechano-chemical Instabilities

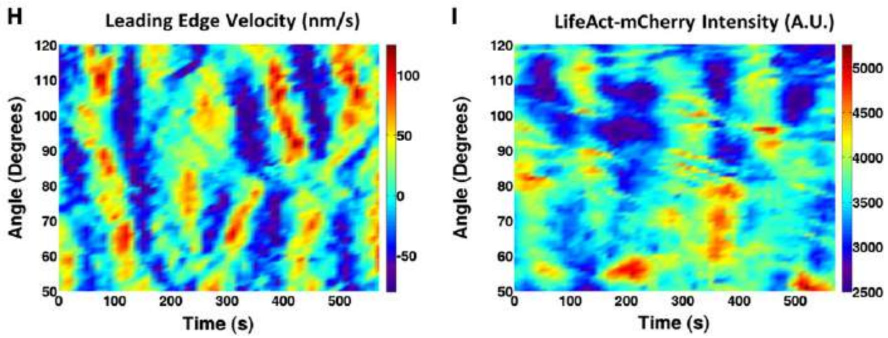


- The leading edge of plated cells shows oscillatory dynamics, and lateral waves.
  - Leading edge velocity anti-correlates with F-actin density



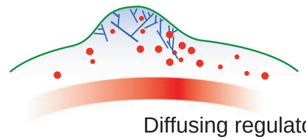


Space independent correlations   Time independent correlations



Gillian L Ryan, et al., and Dimitrios Vavylonis *Biophysical Journal* Volume 102 April 2012 1493–1502

III - Mechano-chemical Instabilities



- Excitable dynamics driven by activator diffusion and fluctuations underlies leading edge dynamics

non-linear autocatalysis

negative feedback

$$\frac{\partial A}{\partial t} = \left(\rho_0 + \rho_2 A^2\right) e^{-F/F_s} - k_A^- A + D_A \nabla^2 A + \sigma(x,t), \quad (1)$$

deactivation diffusion noise

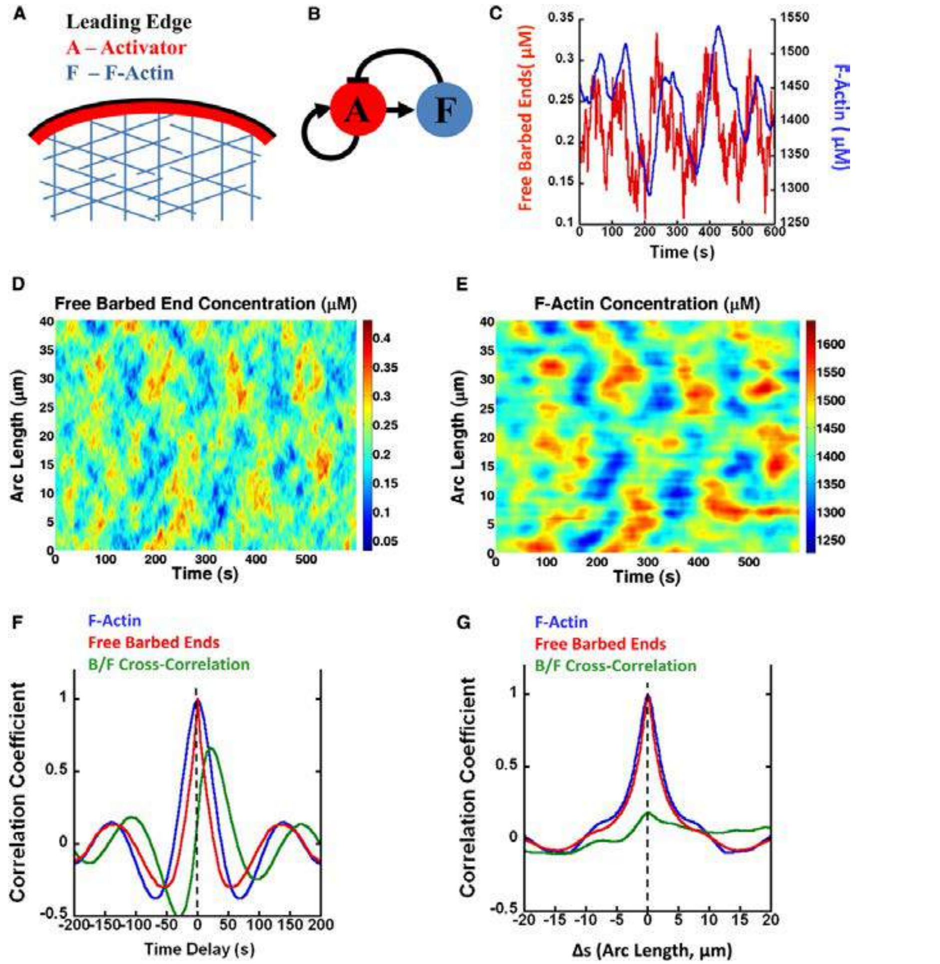
A: activator

B: F-actin barbed ends

F: actin filaments

$$\frac{\partial B}{\partial t} = k_B^+ A - k_B^- B,$$

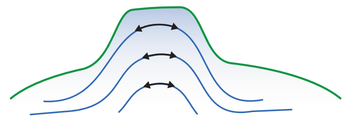
$$\frac{\partial F}{\partial t} = k_F^+ B - k_F^- F.$$



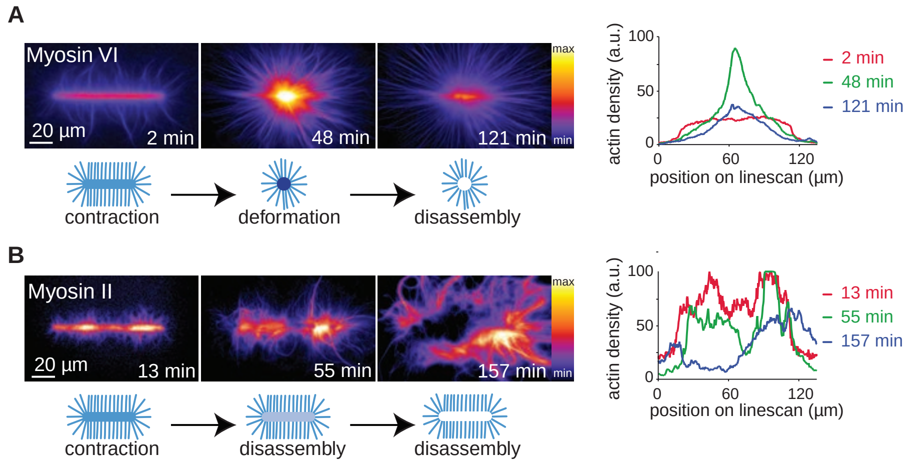
Gillian L Ryan, et al., and Dimitrios Vavylonis *Biophysical Journal* Volume 102 April 2012 1493–1502

III - Mechano-chemical Instabilities

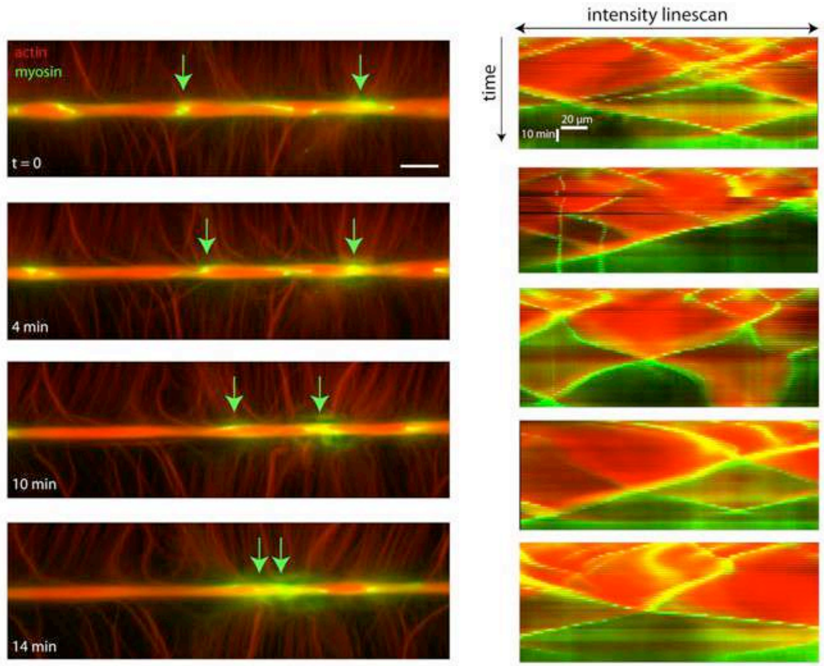
- *in vitro* evidence of tension dependent spatial coupling in wave progressio..
- Contraction (eg. Myosin) induced wave of actin disassembly



- Myosin induces sequential deformation and disassembly of anti-parallel actin filaments



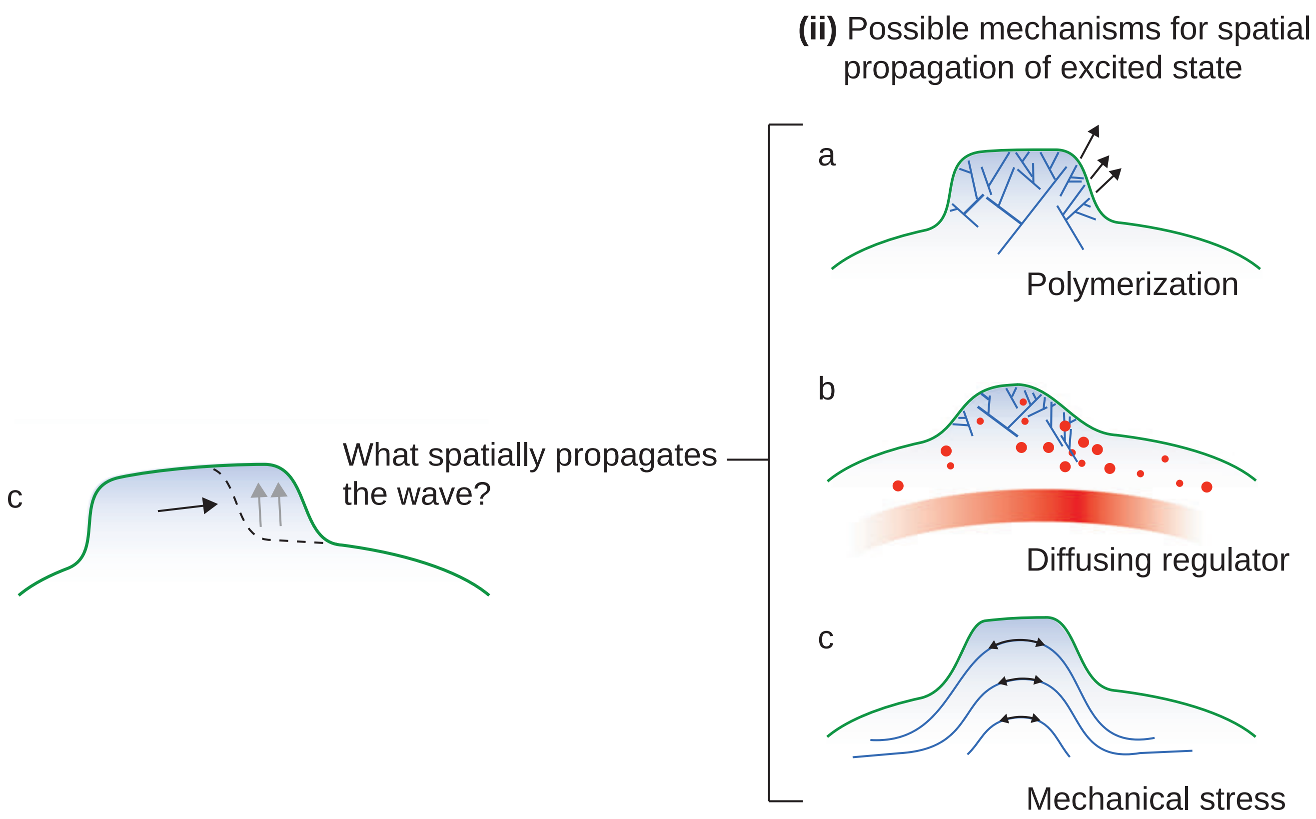
- Myosin induces actin disassembly trigger waves



A-C Reymann, et al., and Manuel Théry, Laurent Blanchoin. *Science*, 336:1310-1314

III - Mechano-chemical Instabilities

Mechano-chemical propagation of trigger waves



Jun Allard and Alex Mogilner. *Current Opinion in Cell Biology* 2013, 25:107-115.

Self-organisation of mechanochemical systems: principles

- Mechano-chemical systems give rise to complex spatial and temporal instabilities across biological scales:

  e.g. spatial patterns, pulsations and trigger waves in actomyosin networks

- Mechanical « Turing-like » instabilities:

  autocatalytic amplification of active stress (advection, non linear effects due to stress/strain dependent activation of stress, effect of orientational order of actin filaments or ECM, etc)

  long range negative feedback: elasticity, friction, diffusion etc.

- Excitability of biochemical network

  autocatalytic amplifications of fluctuations and delayed negative feedback.

  spatial coupling (diffusion of molecule)

  e.g. Rho1GTP oscillations and travelling waves:

- Mechanical feedbacks in excitable systems:

  positive feedback, and/or spatial coupling.

- Mechano-chemical coupling: advection and turnover of active stress regulators

✔ **Length and time scales associated with mechano-chemical information govern these dynamics**

1. Introduction - phenomenology

2. Chemical Instabilities
   21. Spatial instabilities - Turing patterns
   22. Temporal instabilities - Excitability
   23. Spatial-temporal instabilities: waves

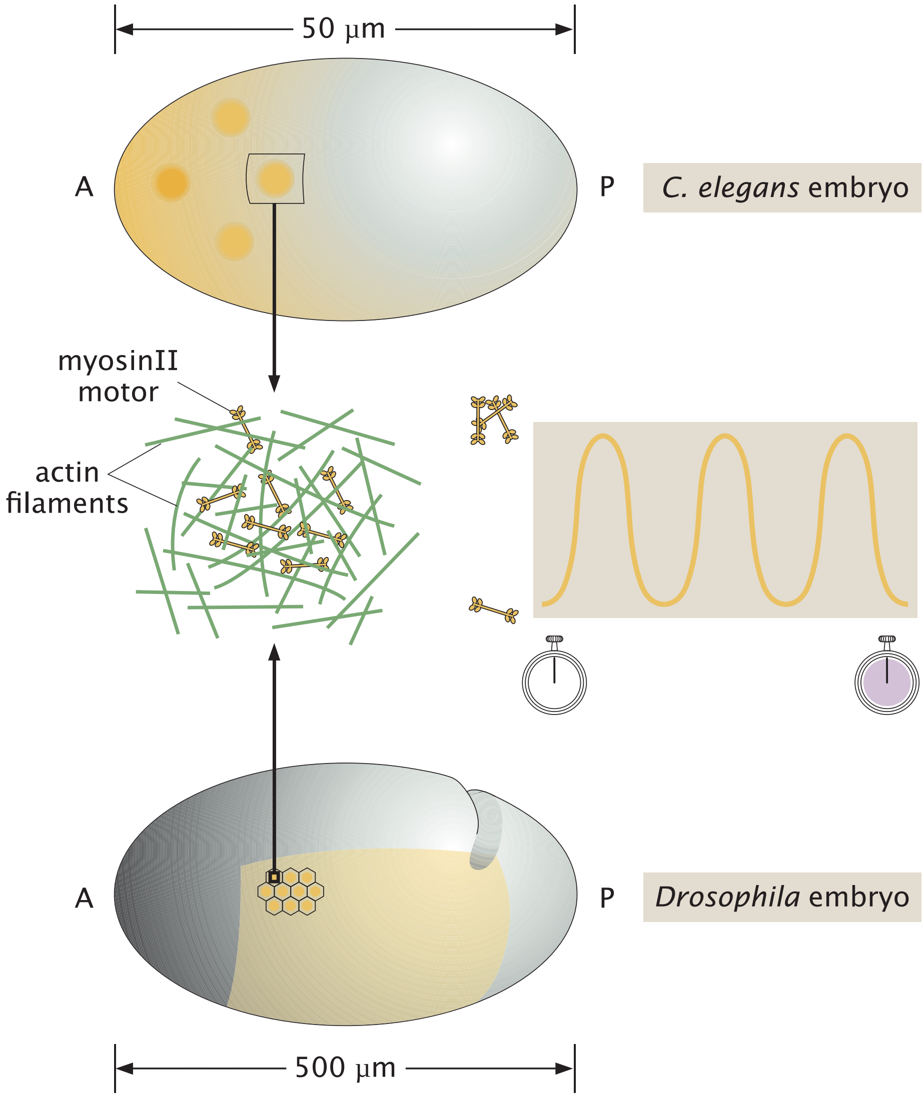
3. Mechanical instabilities
   31. Cellular aggregates: viscoelastic model
   32. Active gel: hydrodynamic and viscoelastic models

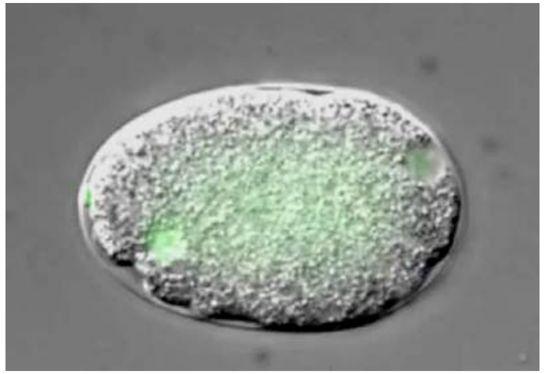
4. Mechano-chemical Instabilities
   41. Mechano-chemical coupling: actomyosin dynamics
   42. Actin based trigger waves

5. Developmental significance: impact on cellular and tissue morphogenesis

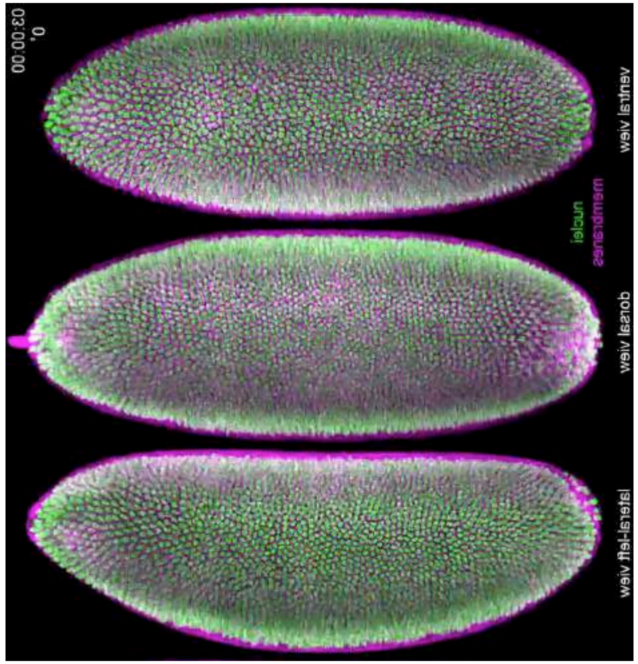
V - Developmental significance

- Embryonic cells exhibit actomyosin pulsations





Gönczy lab, EPFL

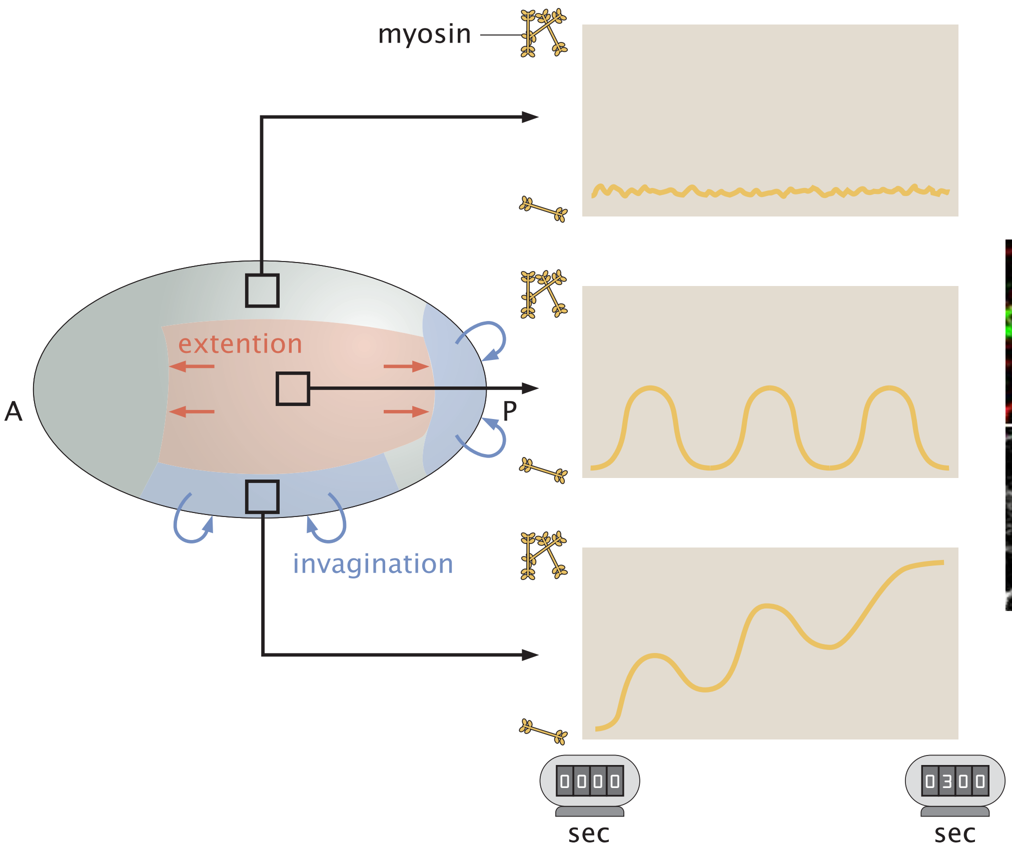


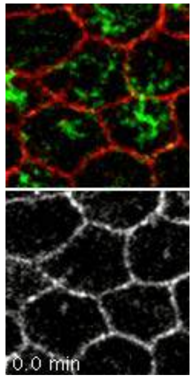
Keller lab, HHMI Janelia Campus

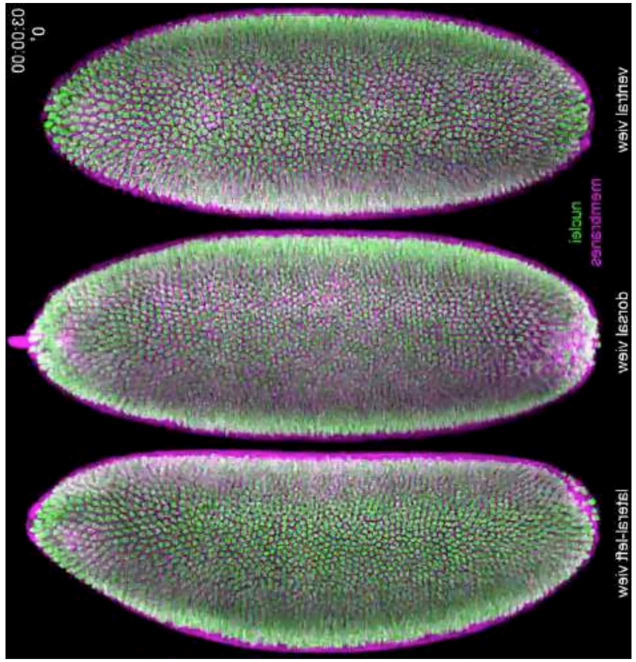
V - Developmental significance

- Impact of pulsatile contractility on cellular and tissue morphogenesis: tissue invagination, tissue extension.

See Courses 11th and 18th December







Keller lab, HHMI Janelia Campus

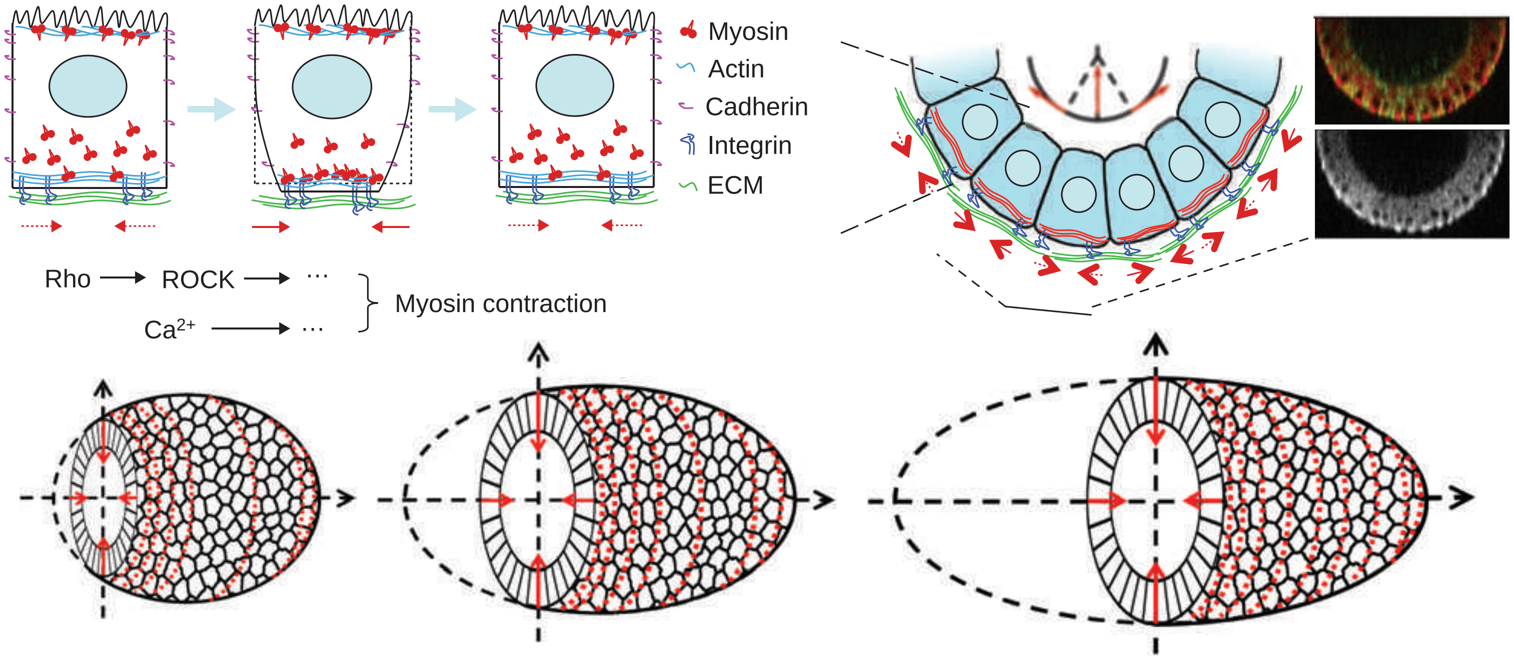
A. Martin,, M. Kaschube and E. Wieschaus, *Nature* (2009) 457:495-499

M. Rauzi, PF Lenne and T. Lecuit, *Nature (*2010) 468:1110-4.

Munjal, A., Philippe, J.-M., Munro, E. & Lecuit, T. *Nature* (2015) 524, 351–355.

V - Developmental significance

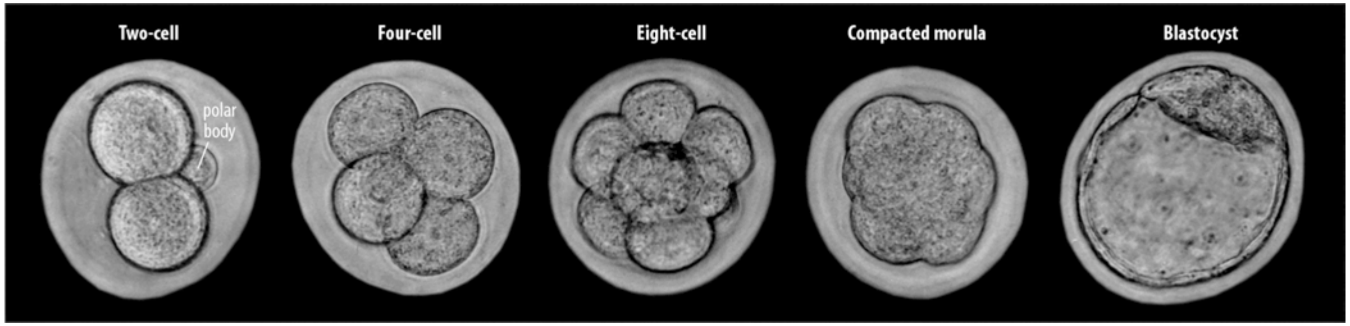
- Impact of pulsatile contractility on cellular and tissue morphogenesis: tissue invagination, tissue extension.



Li He et al. and Denis Montell. *Nature Cell Biology* 2010. 12:1133-1142

V - Developmental significance

- Impact of pulsatile contractility on cellular and tissue morphogenesis: mouse embryo compaction



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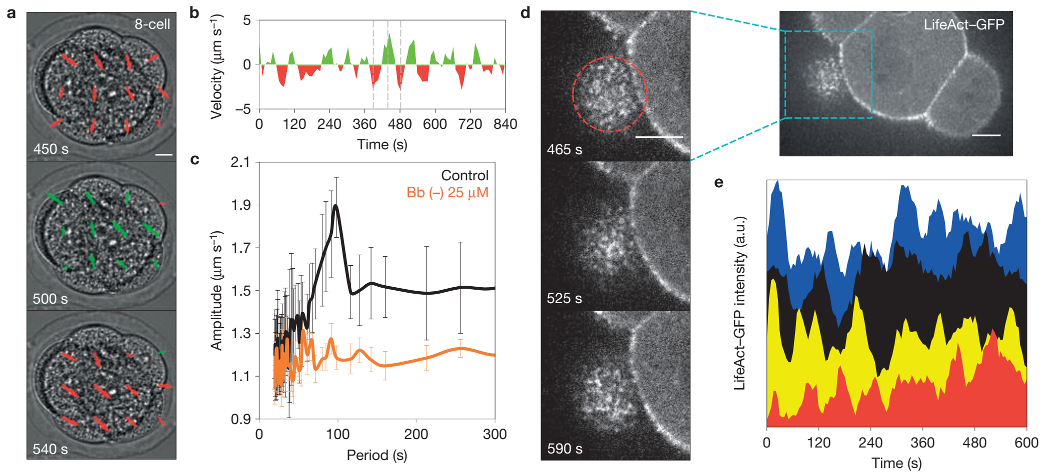

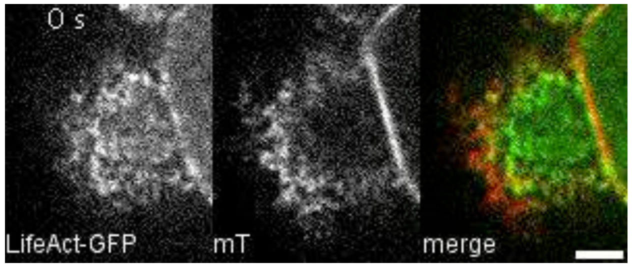

Jean-Léon Maître, R. Niwayama, H. Turlier, F. Nédélec and, T. Hiragii. *Nature Cell Biol*, 336:1310-1314 (2015)

V - Developmental significance

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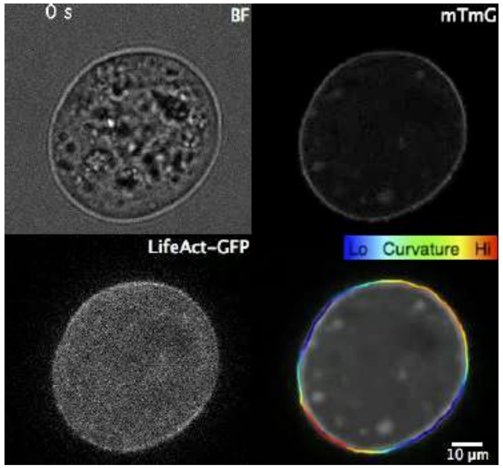
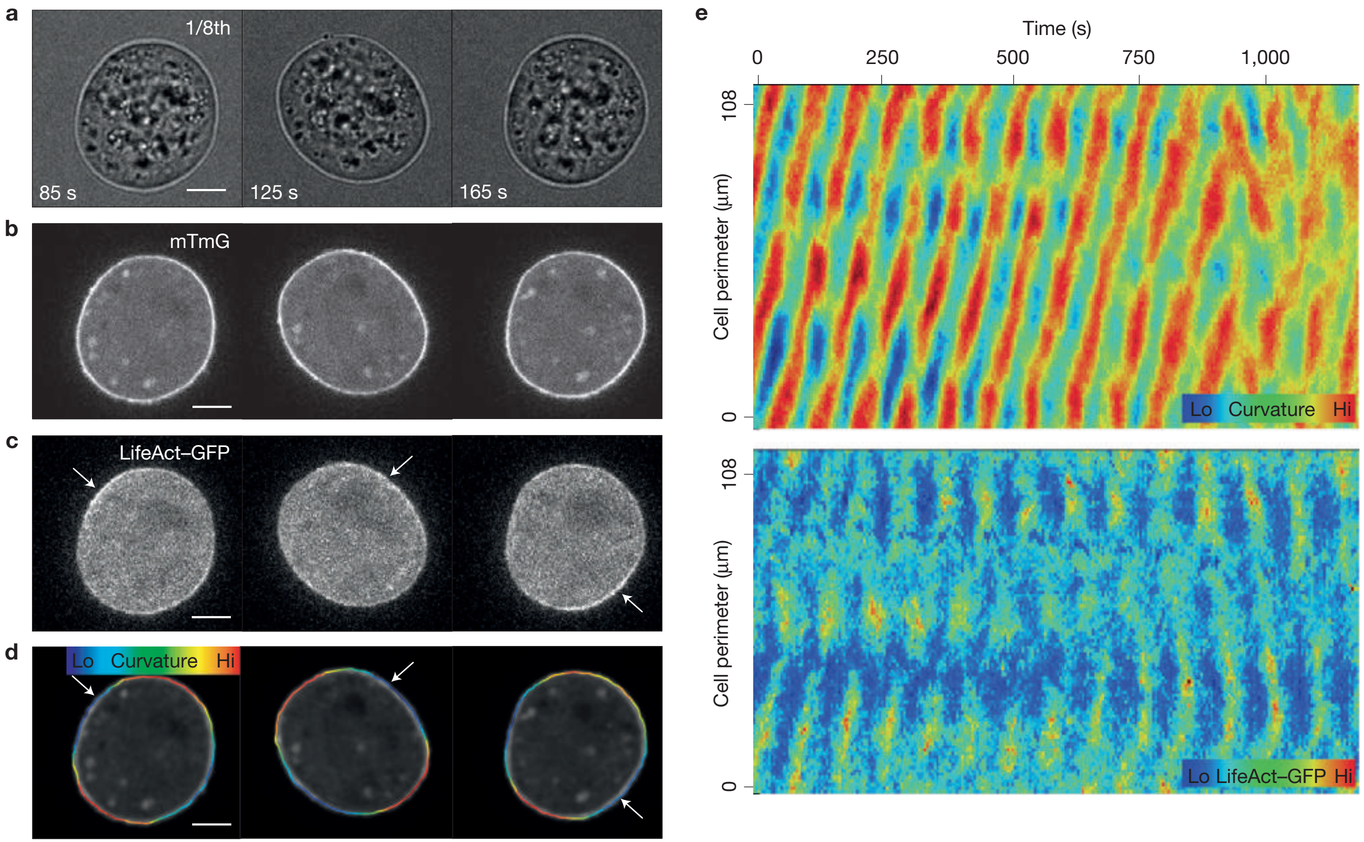




Jean-Léon Maître, R. Niwayama, H. Turlier, F. Nédélec and, T. Hiragii. *Nature Cell Biol*, 336:1310-1314 (2015)

V - Developmental significance

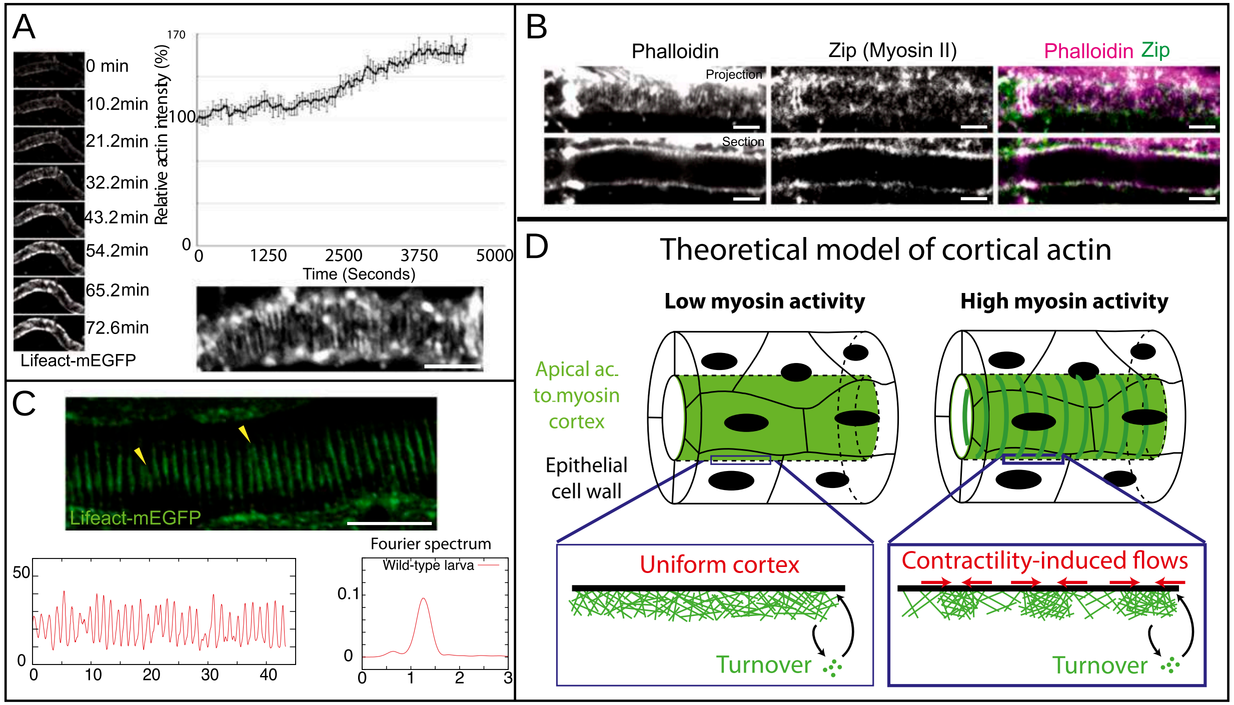
- Spatial patterning by mechano-chemical instabilities during tubulogenesis

Viscous flow of active gel with turnover (of actin):

$$\partial_t \rho = \frac{\rho_0 - \rho}{\tau} - \partial_x(\rho v) + D\partial_{xx}\rho,$$

$$\partial_x \sigma = \xi v \quad \sigma = \chi^0 \rho/\rho_0 + \eta \partial_x v,$$

Contractility must overcome diffusion and frictional resistance to flow



Threshold for Myosin2 contractility leading to instabilities:

$$\chi_c = (\sqrt{\eta/\tau} + \sqrt{D\xi})^2$$

Wavelength of stationary pattern:

$$\lambda_c = 2\pi \left(\frac{D\tau\eta}{\xi}\right)^{1/4}.$$

E. Hannezo et al S. Hayashi and J-F. Joanny. *PNAS* 112:8620–8625 (2015)

see also: J. Bois, F. Jülicher and SW. Grill. *PRL*. 2011. 106, 028103

V - Developmental significance

- Spatial patterning by mechano-chemical instabilities during tubulogenesis

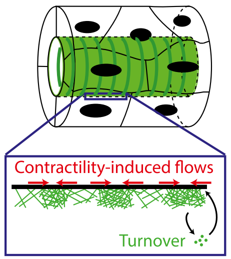
Experimental tests of the model using mutants that are expected to affect friction of the actin network with the cell boundaries:

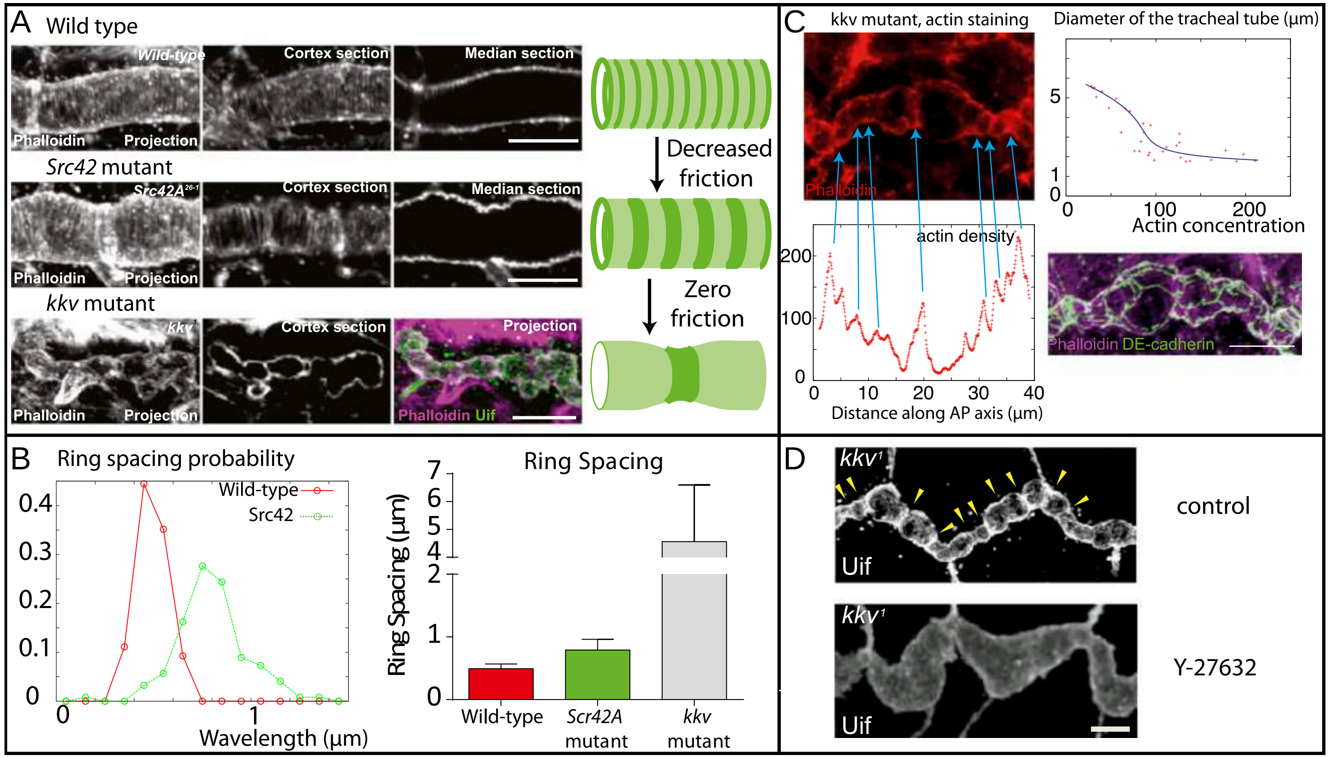
Wavelength of stationary pattern:

$$\lambda_c = 2\pi \left(\frac{D\tau\eta}{\xi}\right)^{1/4}.$$

Defects in E-cadherin adhesion complexes

Defects in ECM linkages: chitine synthase





E. Hannezo et al S. Hayashi and J-F. Joanny. *PNAS* 112:8620–8625 (2015)

V - Developmental significance

- Pulsatory and wave of cell contractions reveal the out of equilibrium nature of cell and tissue morphogenesis.

  e.g. apical cell constriction during tissue internalisation and invagination.
  cell intercalation during tissue flow and extension.

- Biological function:
  1. Pulsations prevent geometrical trap and favour exploration of cellular configurations (active noise).

  2. Tissue viscoelasticity: time scale of deformations (set by pulses period) vs timescale of dissipation
  3. Enables collective dynamics: non synchronous behaviour
  4. Trigger waves enable rapid, long range communications
  5. Trigger waves confer adaptation to environment (cell motility)

- Implication of self-organisation: high complexity of behaviours from low level developmental information.

Self-organization

- local and direct interactions
- few rules and parameters

✓ Complexity emerges from very simple rules
The amount of information required to model/encode is very small

Next Course

Tissue curvature: control and self-organisation