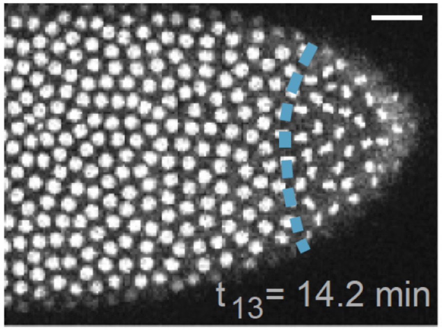
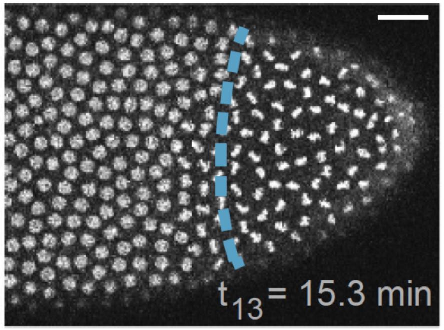
The nature of waves in the early embryogenesis of *Drosophila melanogaster*

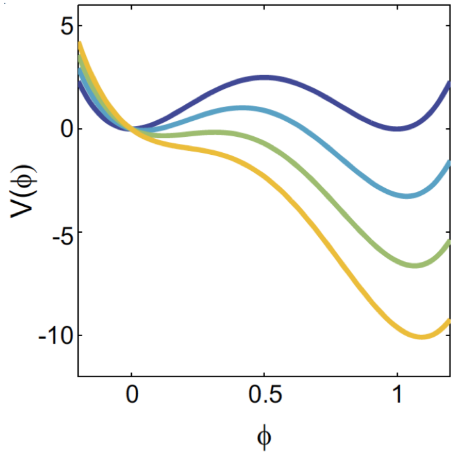
UCSD

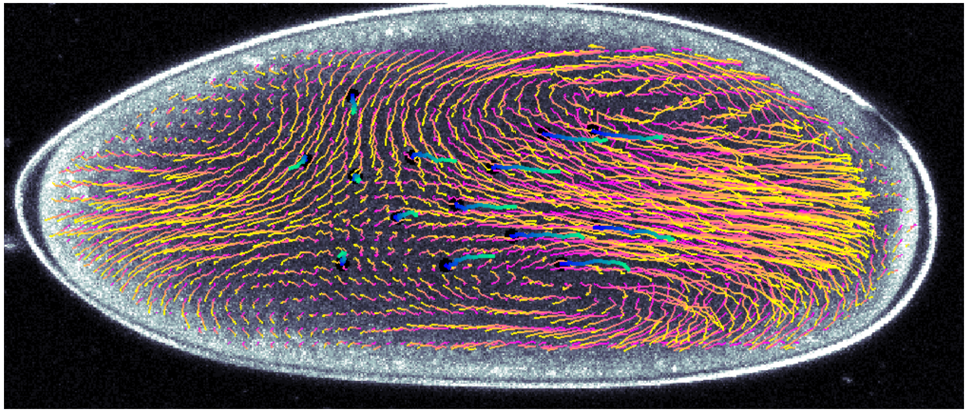
Massimo Vergassola

Physics Department

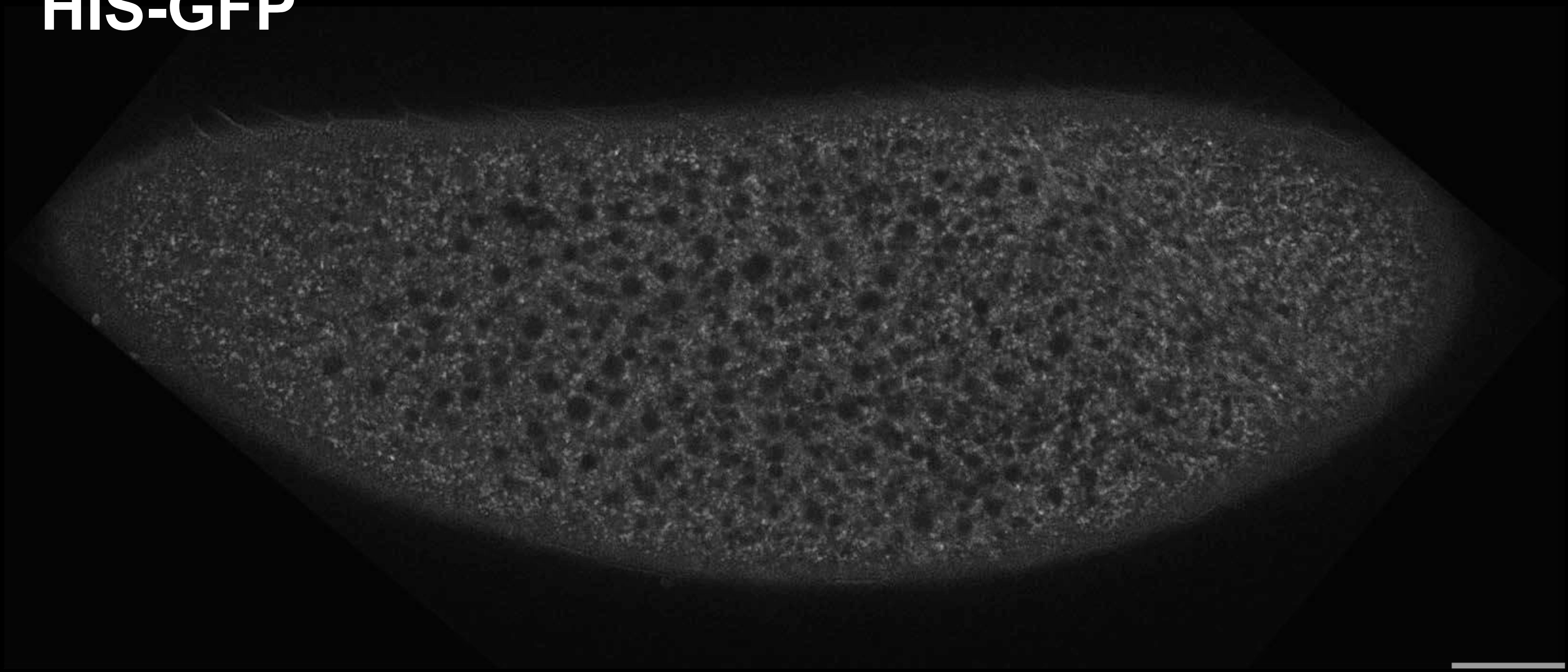






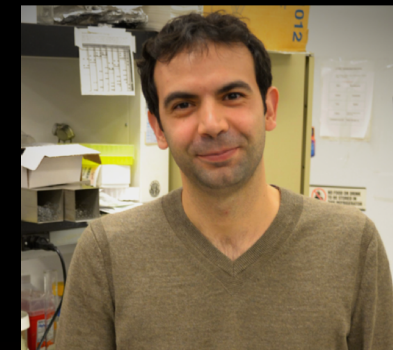


Visualizing the early steps of embryogenesis

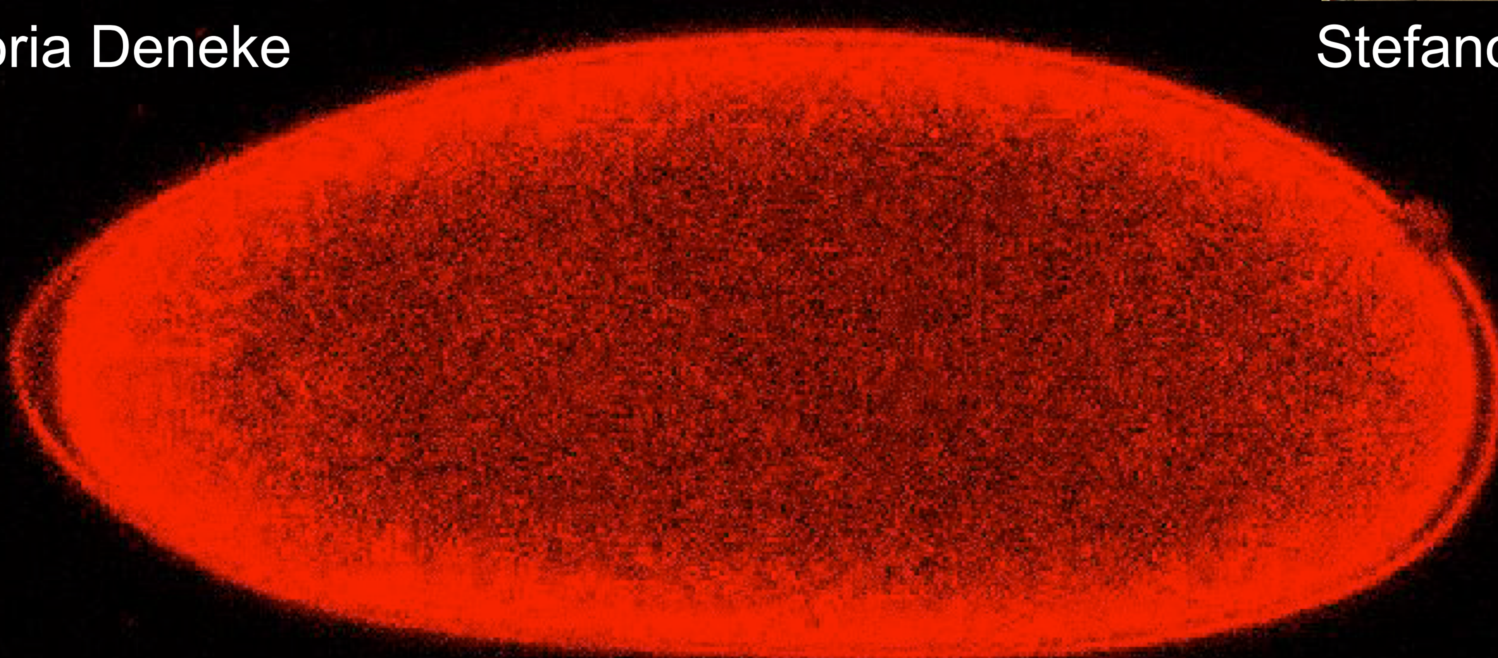


Imaging nuclear spreading

Victoria Deneke



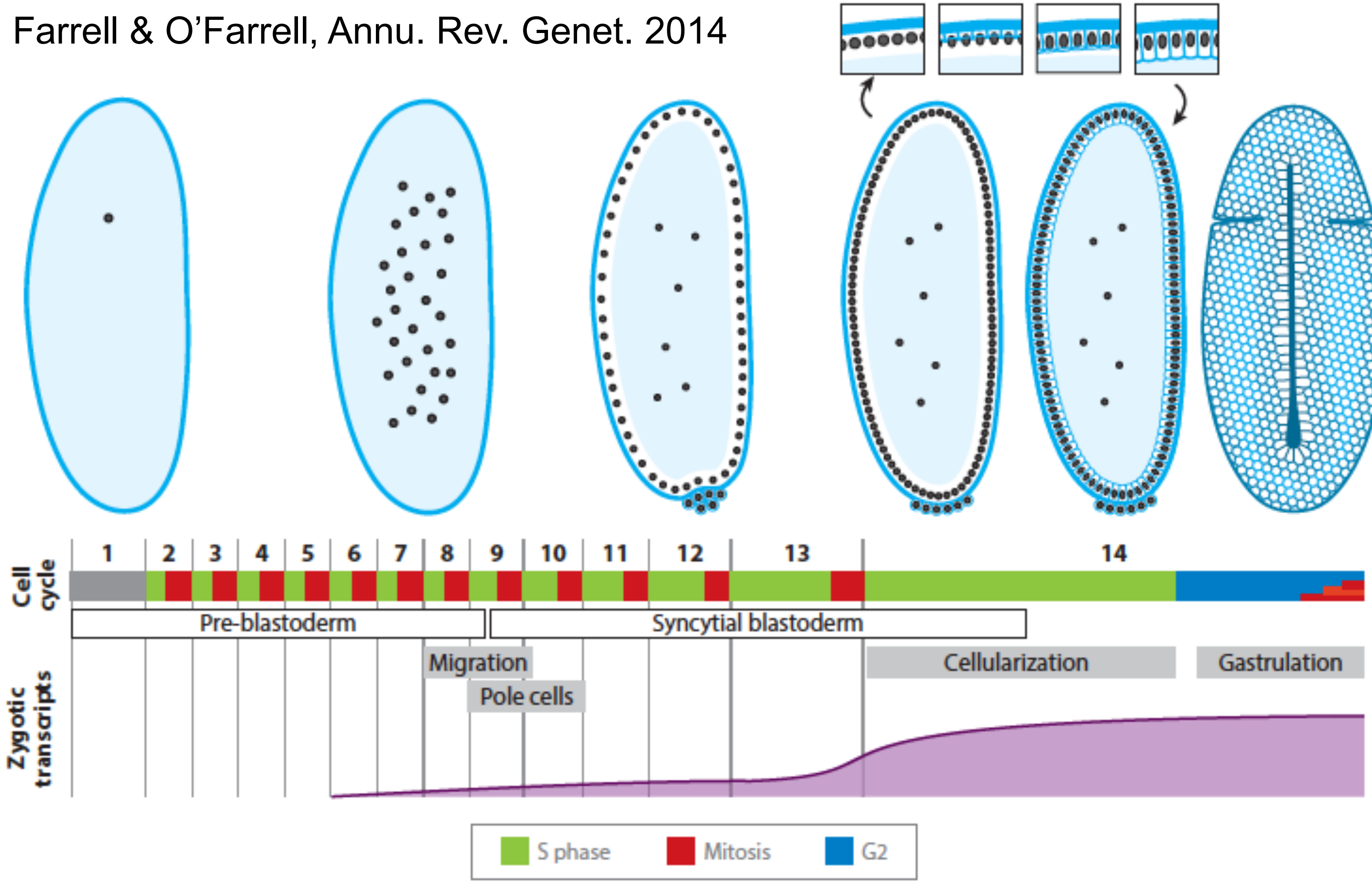
Stefano di Talia



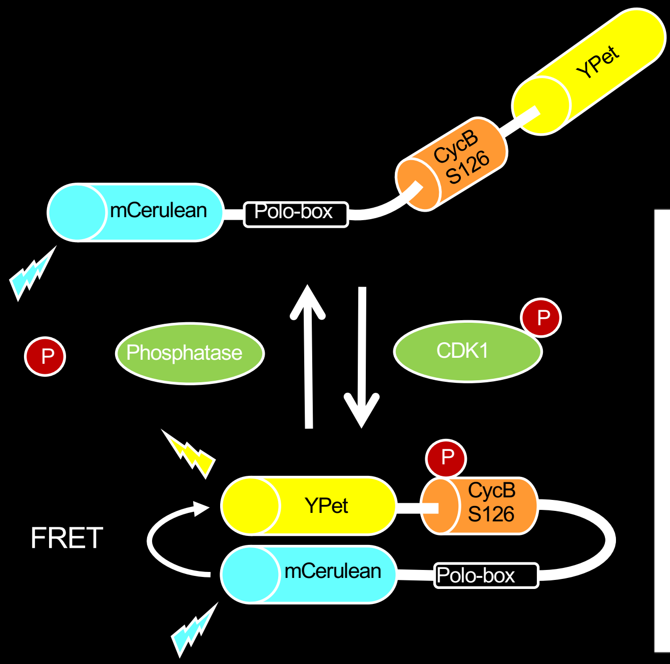
PCNA RFP

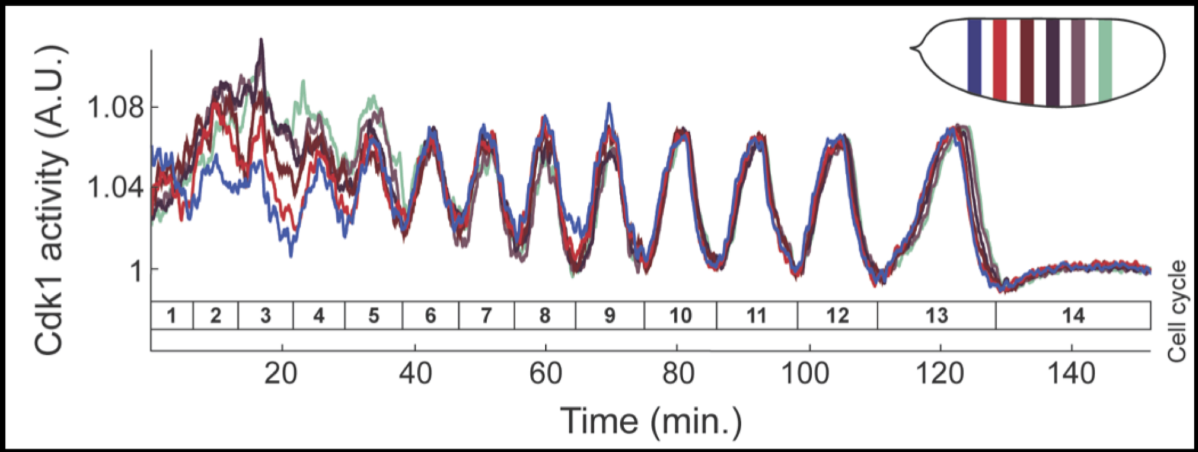
Schematics of the very first hours

Farrell & O'Farrell, Annu. Rev. Genet. 2014



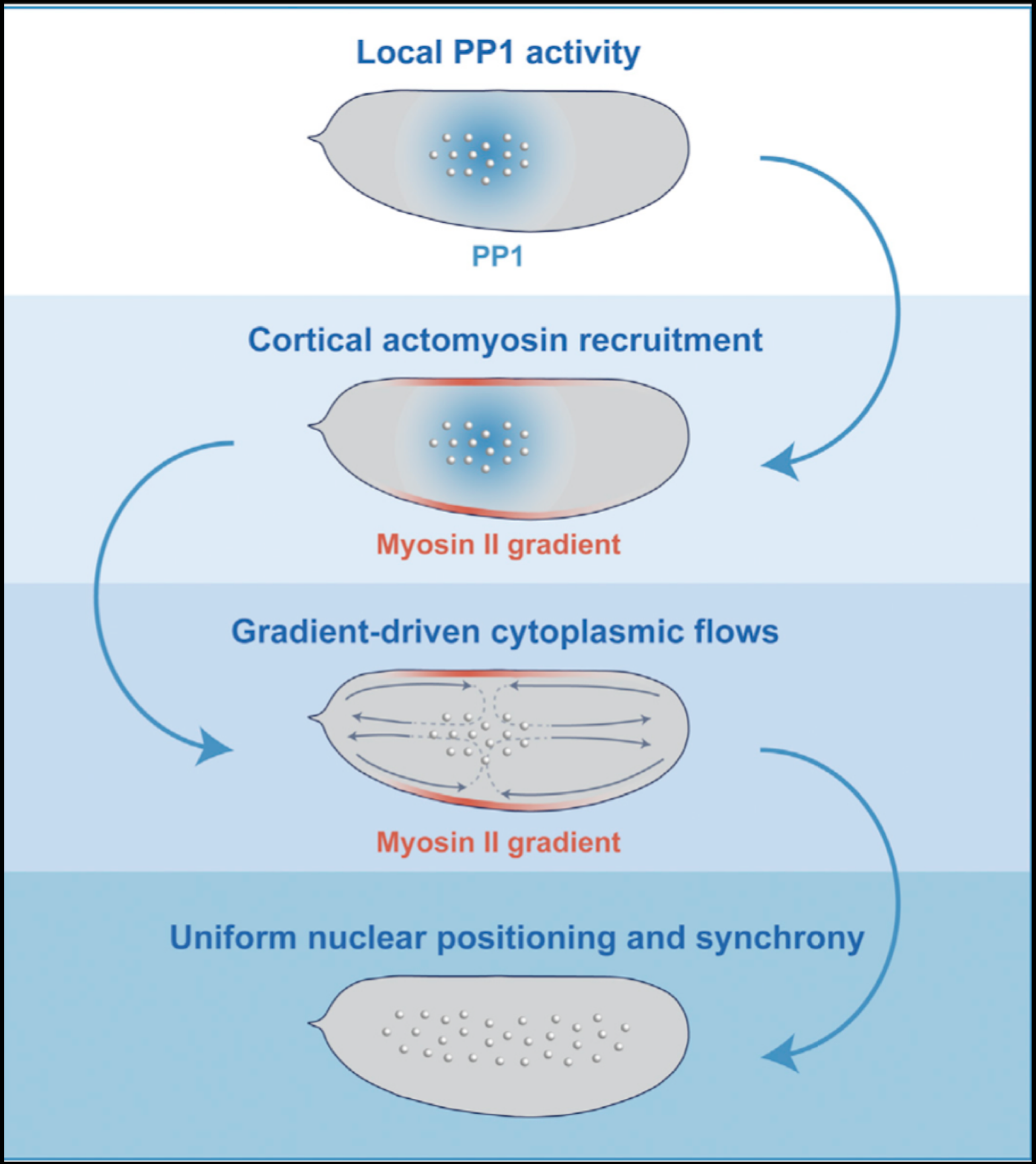
An *in vivo* biosensor for Cdk1 activity





Gavet and Pines Dev Cell and JCB 2010

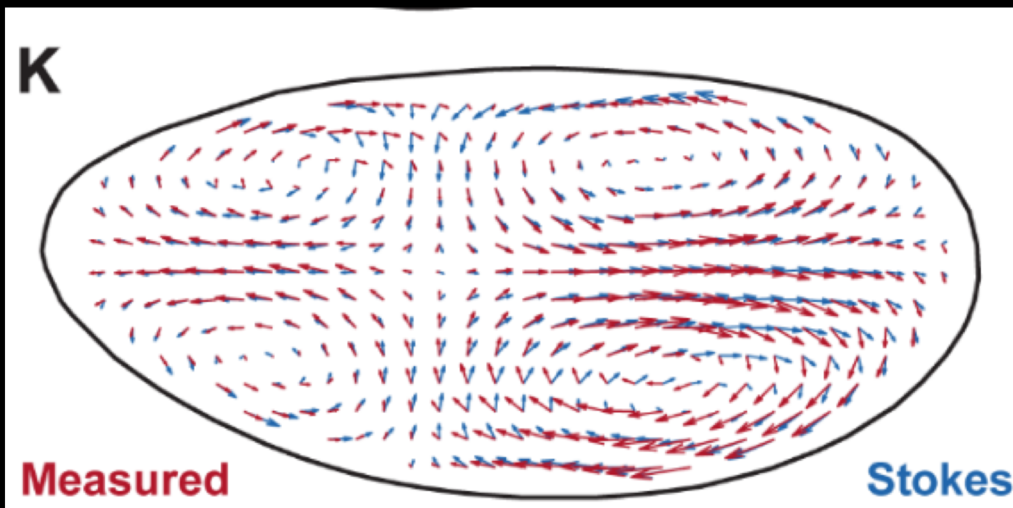
Deneke et al Dev Cell 2016



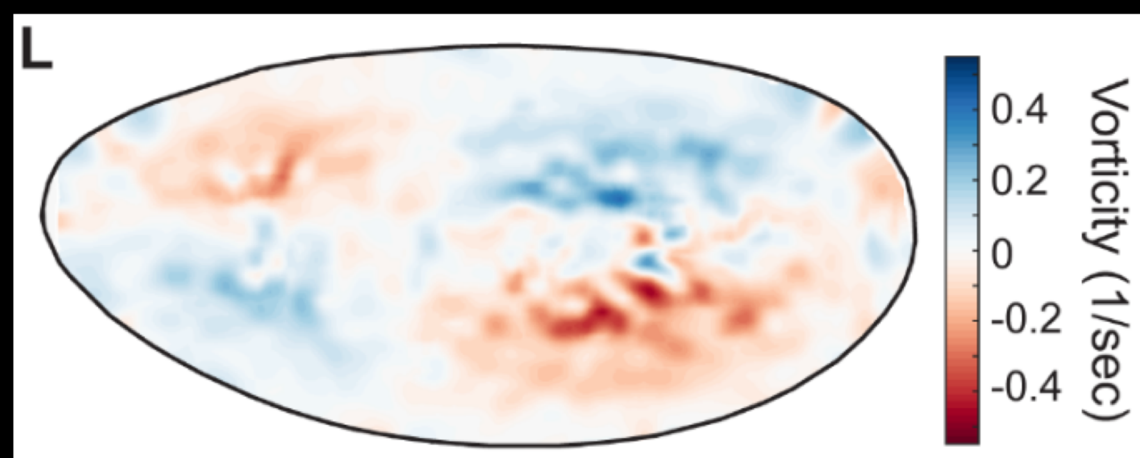
Scheme of the chemical-mechanical coupling controlling the early flow

Deneke et al., Cell, '19

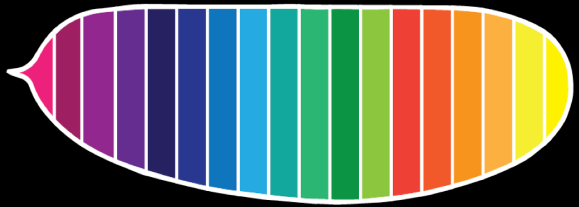
Coupling boundary (cortex) motion with bulk (cytoplasmic and nuclear) flows is "well" captured by Stokes dynamics

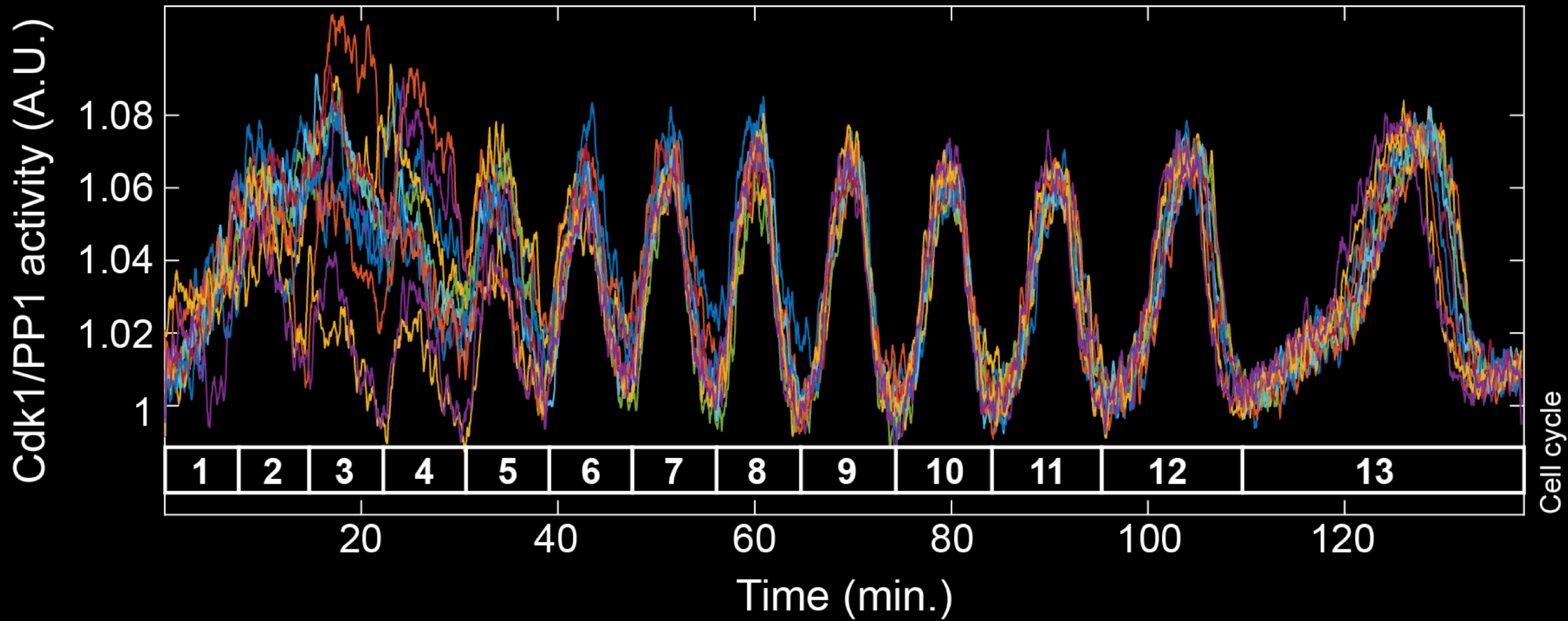


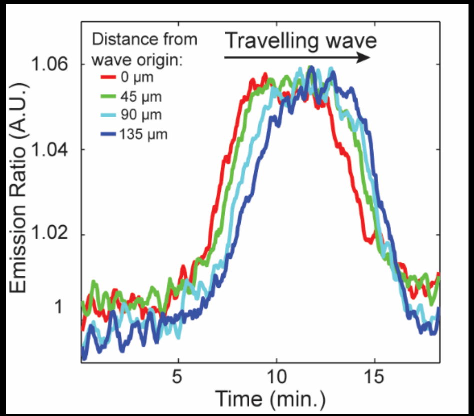
Deneke et al., Cell, '19

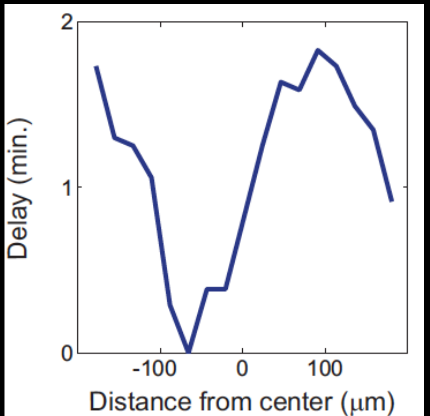


Spatial features of Cdk1 "late" regular oscillations



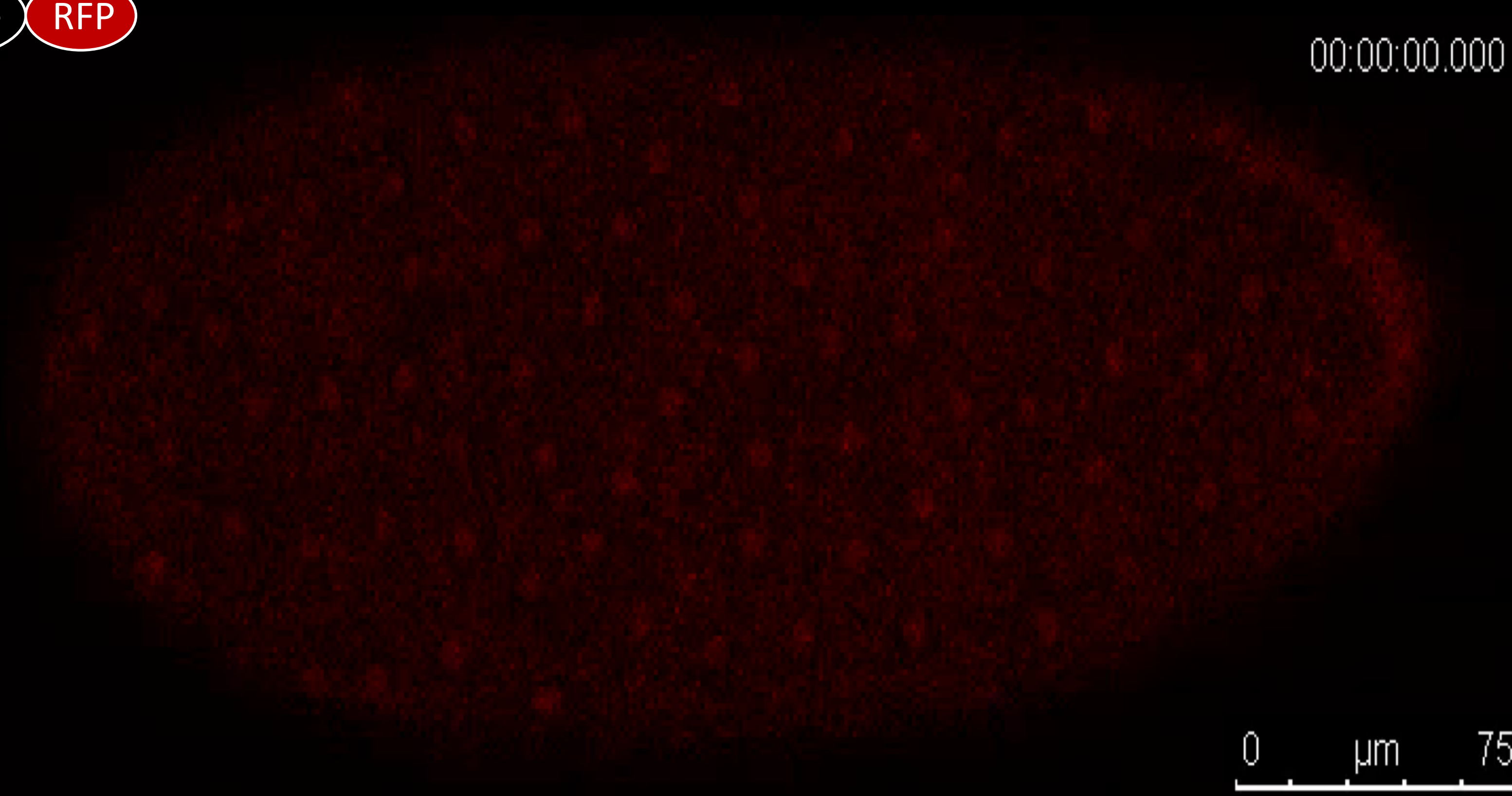






What is the mechanism of these waves and their relation to division waves?

Histone RFP



~500µm

Covered in hours by diffusion with $D=10\mu m^2/s$

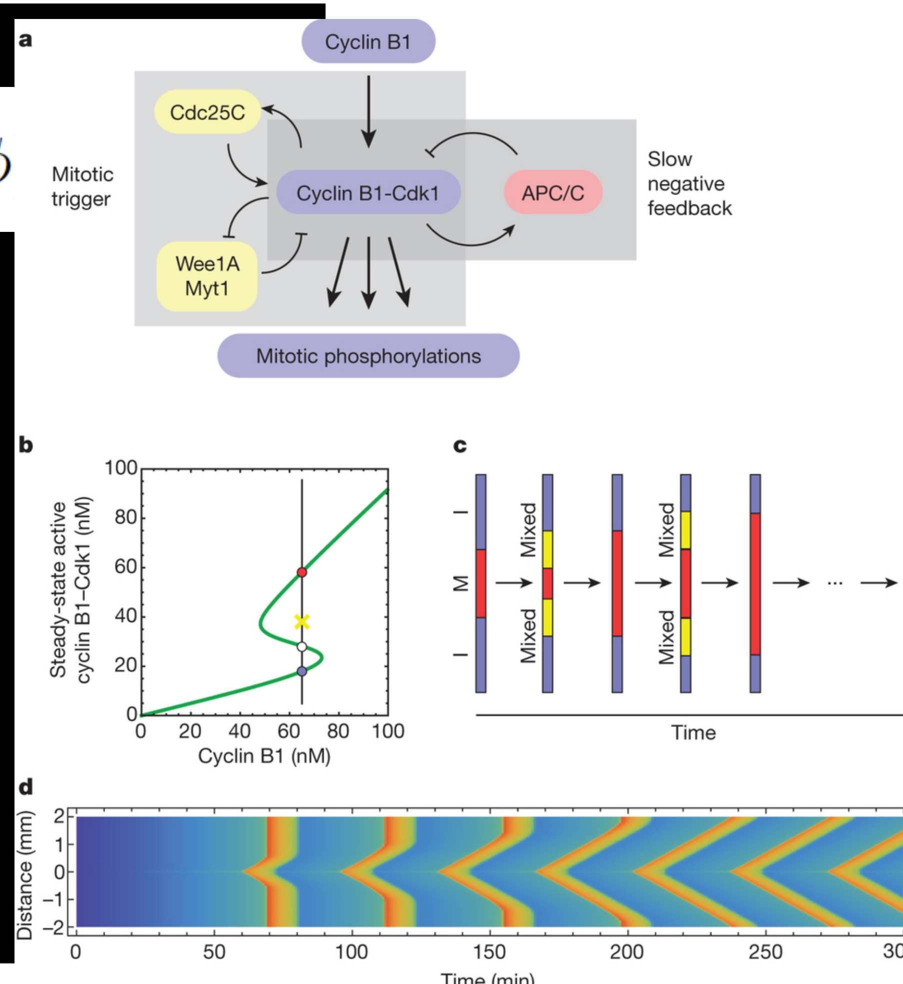
Bistable waves

$$\frac{\partial \phi\left(\boldsymbol{x},t\right)}{\partial t} = D\Delta\phi\left(\boldsymbol{x},t\right) + F(\phi$$

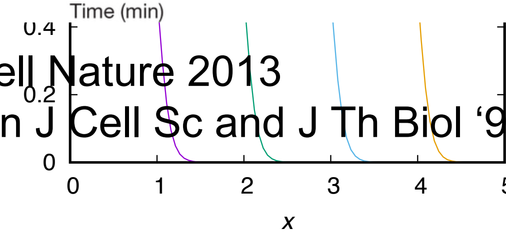
$$F\left(\phi\right) = -\frac{\partial V}{\partial \phi}$$

[redacted] stable point) generates chemical pushed waves

van Saarloos, W Phys. Reports 301, 9-43, (1998).

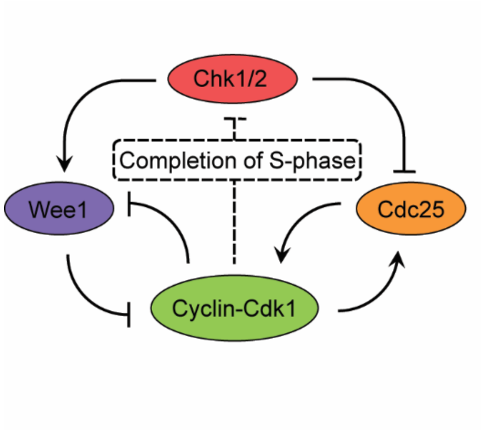


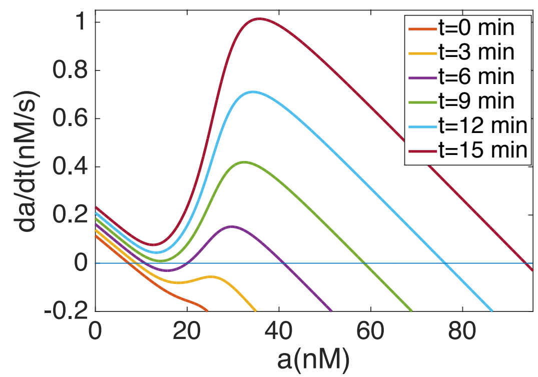
Chang and Ferrell Nature 2013
Novak and Tyson J Cell Sc and J Th Biol ‘93

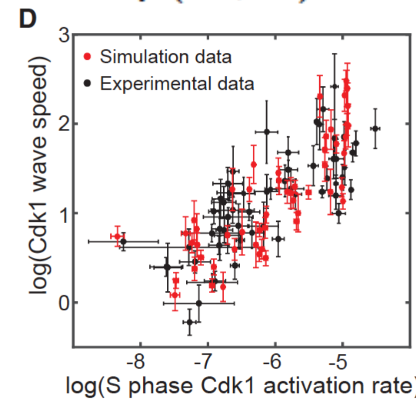


Reaction-Diffusion (GL) for *Drosophila*

$$\partial_t \phi(x,t) = D\nabla^2 \phi(x,t) + F(\phi,t) + \sqrt{2\nu}\,\eta(x,t)$$



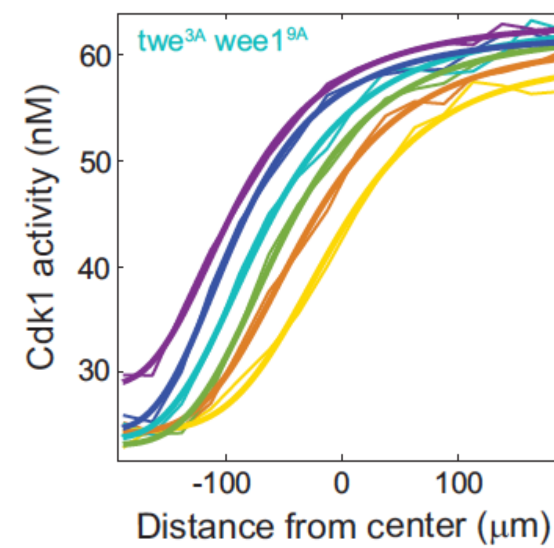




Cues that static picture ought to be revisited

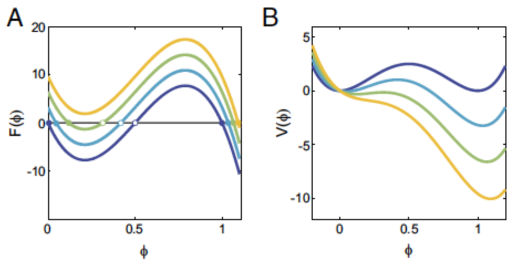
Force changes substantially over a single cycle, i.e. it is strongly time-dependent
(molecular & functional reasons)

Bistable waves are too slow
(potential frozen in time during the bistable phase)



Same phenomenology observed in classical cubic models

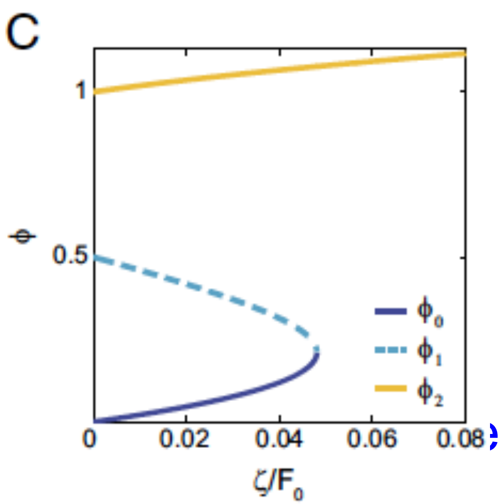
$$\partial_t \phi(x,t) = D\nabla^2 \phi(x,t) + F(\phi,t) + \sqrt{2\nu}\,\eta(x,t)$$



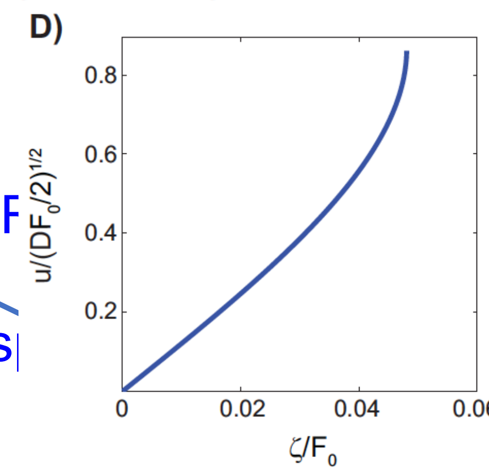
$$F(\phi,t) = -F_0\phi\left(\phi - \frac{1}{2}\right)(\phi - 1) + \zeta(t)$$

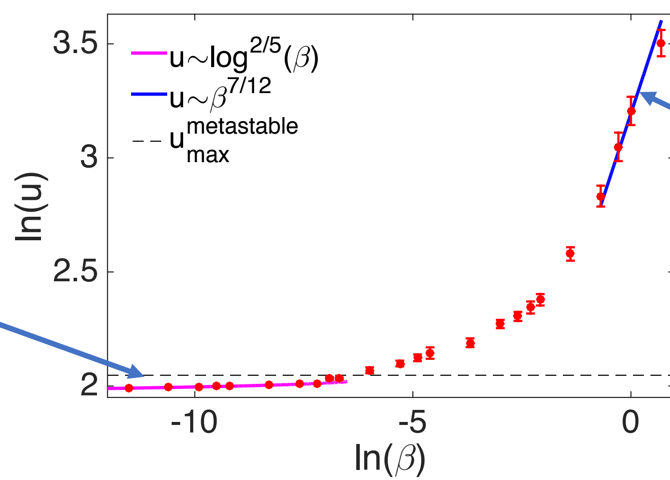
$$\zeta(t) = \beta t$$

For fixed ζ, analytical solution for bistable waves (see Ben-Jacob et al 1985)

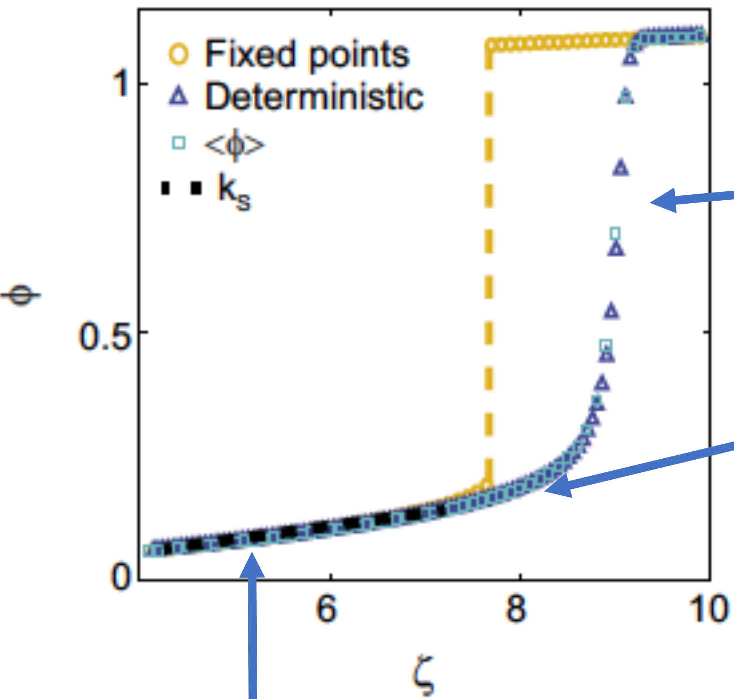


$$F(\phi,t) = -F_0(\phi - \phi_0)(\phi - \phi_1)(\phi - \phi_2)$$





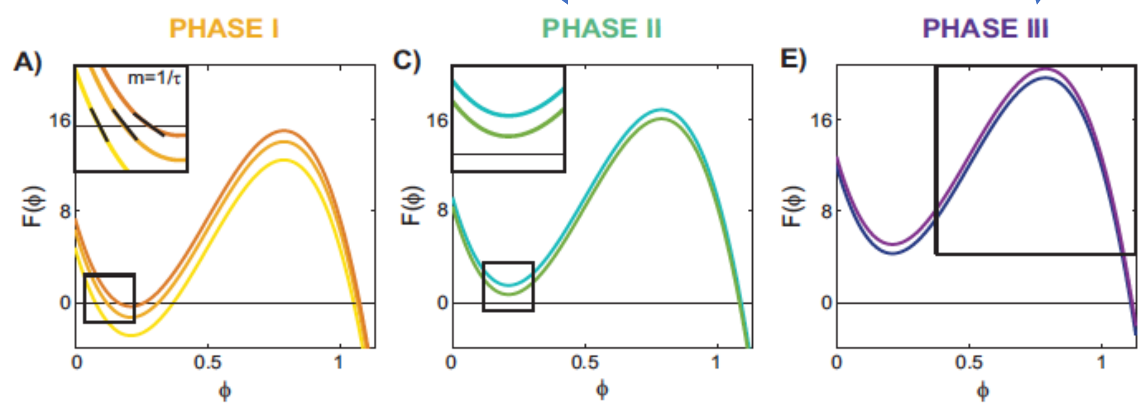
Scheme of the fast-driven dynamics



Phase III (delay-preserving)

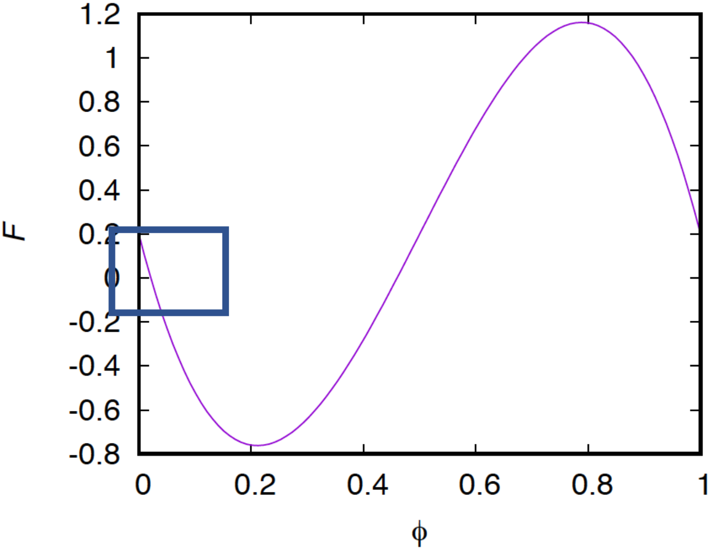
Phase II (sweep waves)

Phase I (quasi-adiabatic)



M. Vergassola, V. Deneke, S. di Talia, PNAS, '18

Phase I: quasi-adiabatic



Slope around fixed point steep: fluctuations induced by noise relax rapidly

$$\partial_t \phi(x,t) = D\nabla^2\phi(x,t) - \frac{\phi - \phi_0}{\tau} + \sqrt{2\nu}\,\eta(x,t)$$

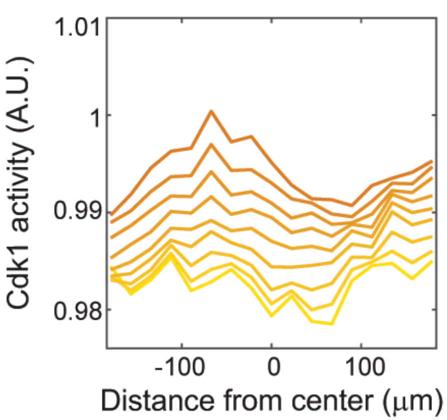
$$C(x) = \langle (\phi(x) - \phi_0)(\phi(0) - \phi_0) \rangle$$

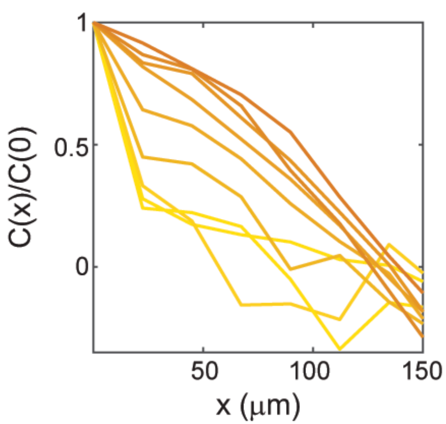
NB: Correlation length is not purely diffusive

$$C(x) = C(0)e^{-\frac{|x|}{\lambda}}\;; \quad \lambda = \sqrt{D\tau}\,; \quad C(0) = \frac{\nu}{2}\sqrt{\frac{\tau}{D}}$$

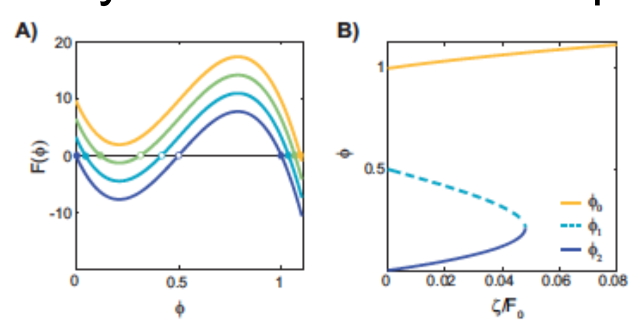
Uhlenbeck-Ornstein (in space)

Increase with time well visible in data

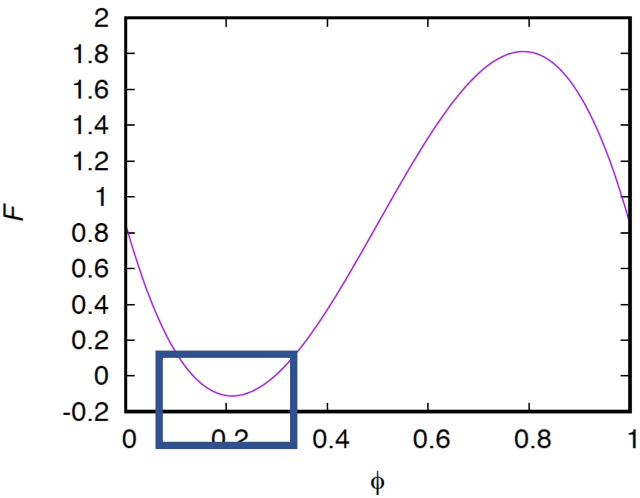




Quasi-adiabatic approximation valid only far from the critical point



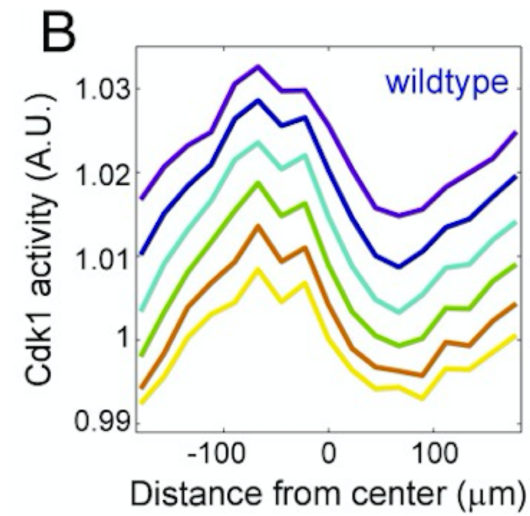
Phase II: Synchronous growth

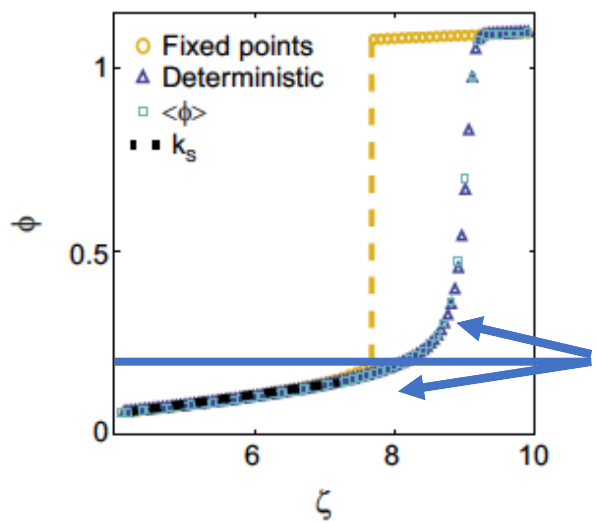


Around the minimum

$$F \simeq -F^* + \gamma(\phi - \phi^*)^2 + \zeta$$

Growths are synchronous ($\phi(x) + f(t)$, with *f* quadratic): spatial gradients are conserved



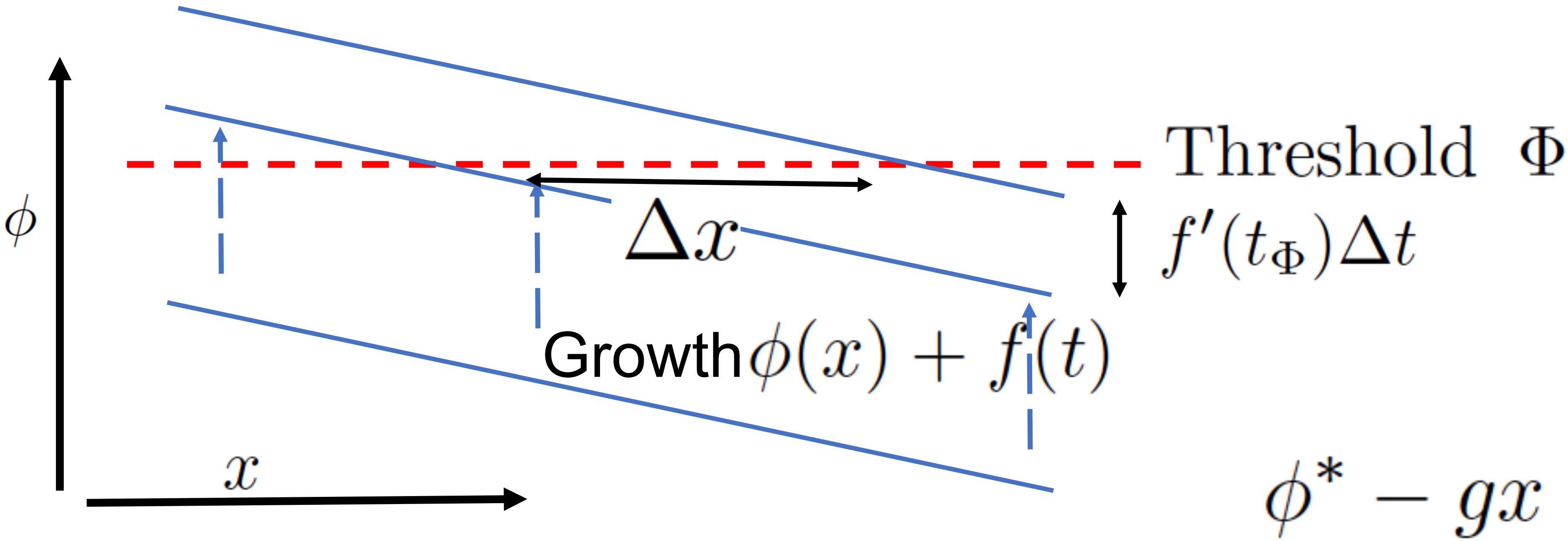


Phase II

The quadratic term is negligible for a window $\propto \beta^{2/3}$ around the knee

Mechanism for wave-like spreading

Delays in passing a threshold among spatial points?



Wave speed

$$u = \frac{f'(t_\Phi)}{g}$$

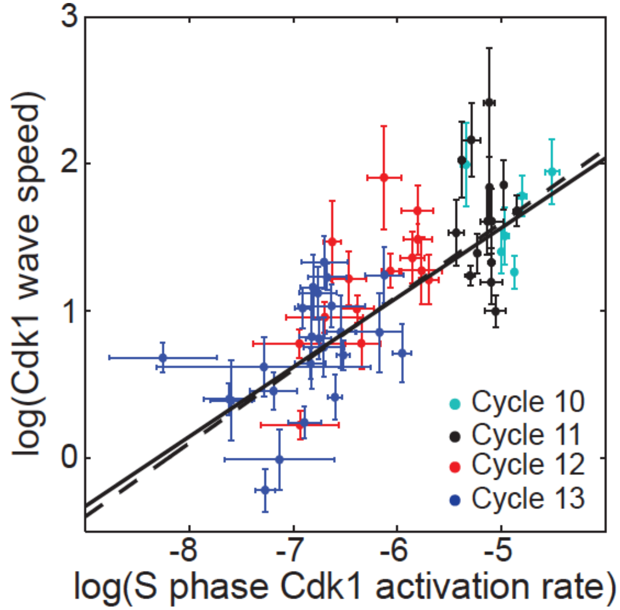
$$g \sim \sqrt{C(0)}/\lambda$$

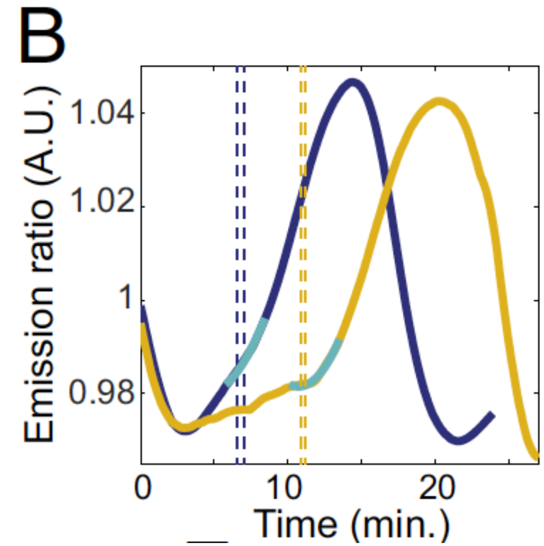
$$\bar{\zeta}_{\overline{\Phi}} - F^* \sim F_0 \left(\beta/F_0^2\right)^{2/3}$$

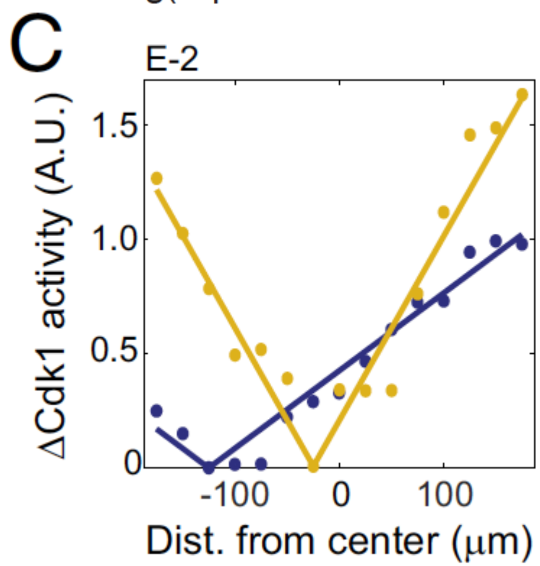
$$u \sim \frac{\beta^{\frac{7}{12}} D^{\frac{3}{4}}}{\nu^{\frac{1}{2}} F_0^{\frac{5}{12}}}$$

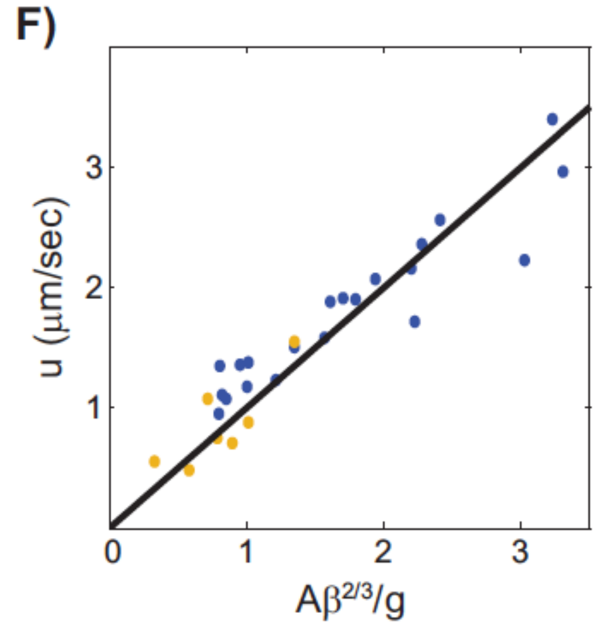
Theoretical predictions *vs* experiments

Dependence on β consistent with 7/12 power (certainly not weak as for bistable)





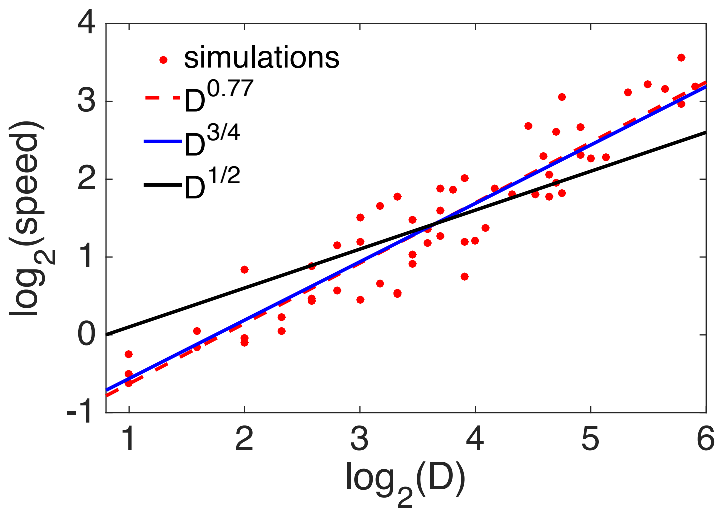




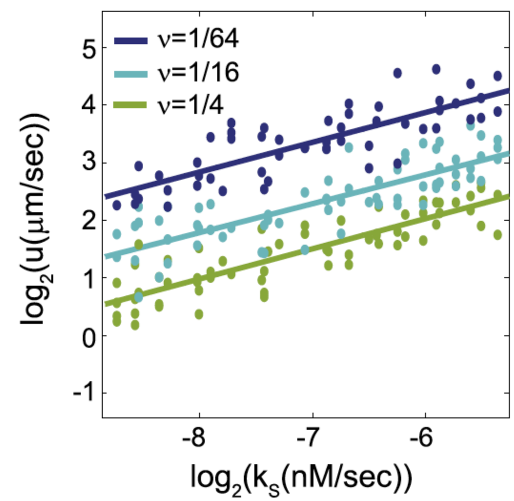
Theoretical predictions *vs* model

$$u \sim \frac{\beta^{\frac{7}{12}} D^{\frac{3}{4}}}{\nu^{\frac{1}{2}} F_0^{\frac{5}{12}}}$$

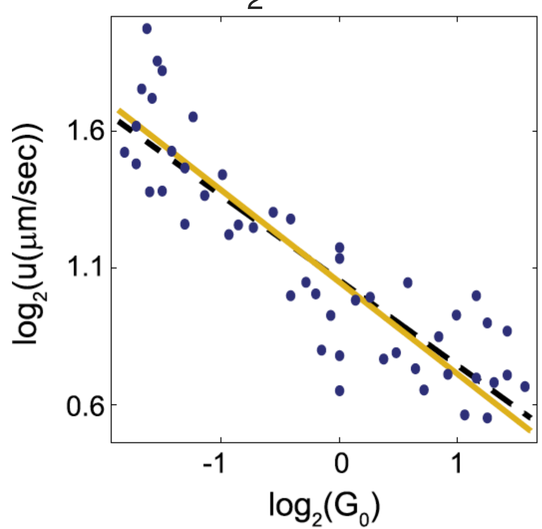
¾ power in D



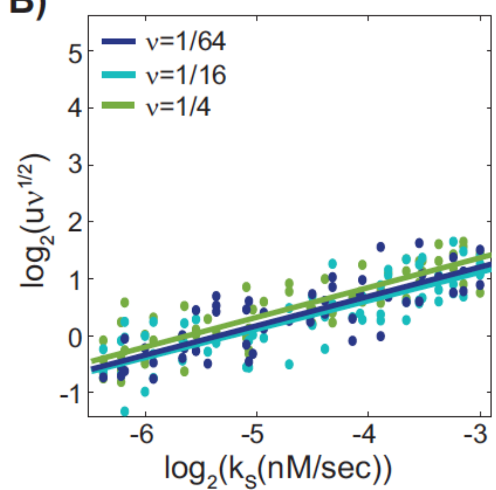
-1/2 power amplitude noise



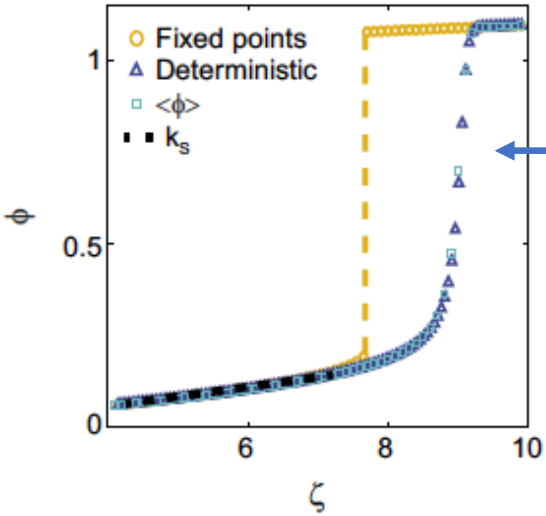
-1/3 power in amplitude



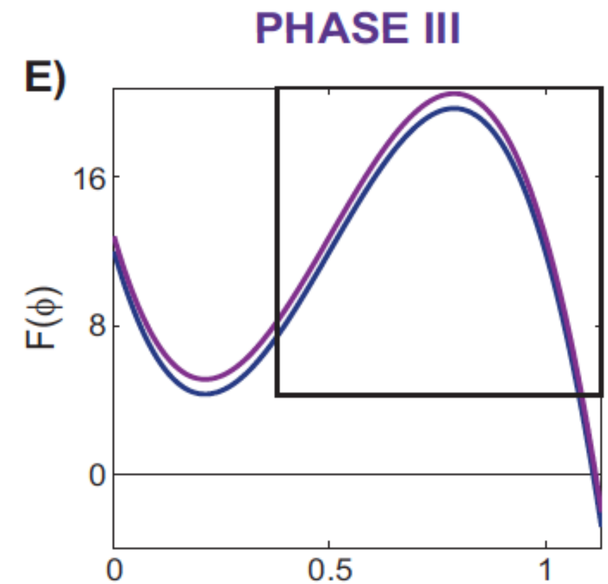
B)



Phase III: rapid autonomous growth



Phase III

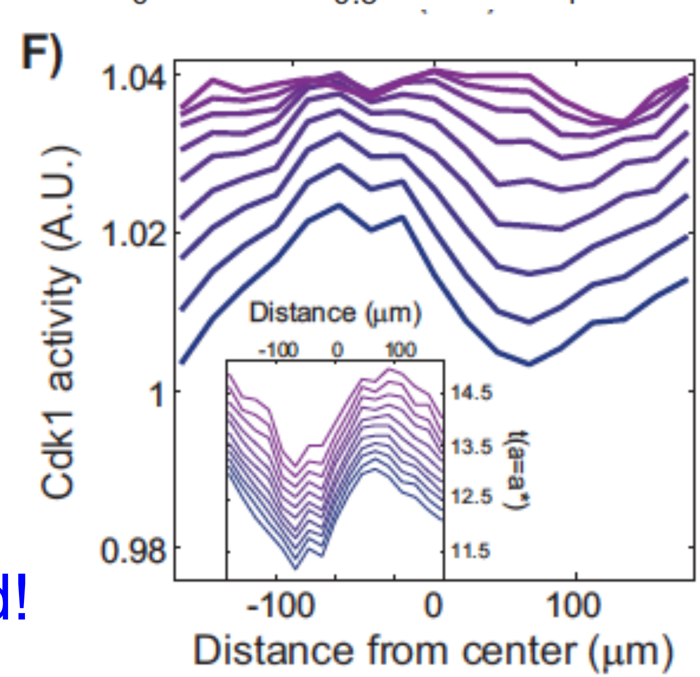


Forces are substantial and their relative change in time is minor

Growths are largely autonomous

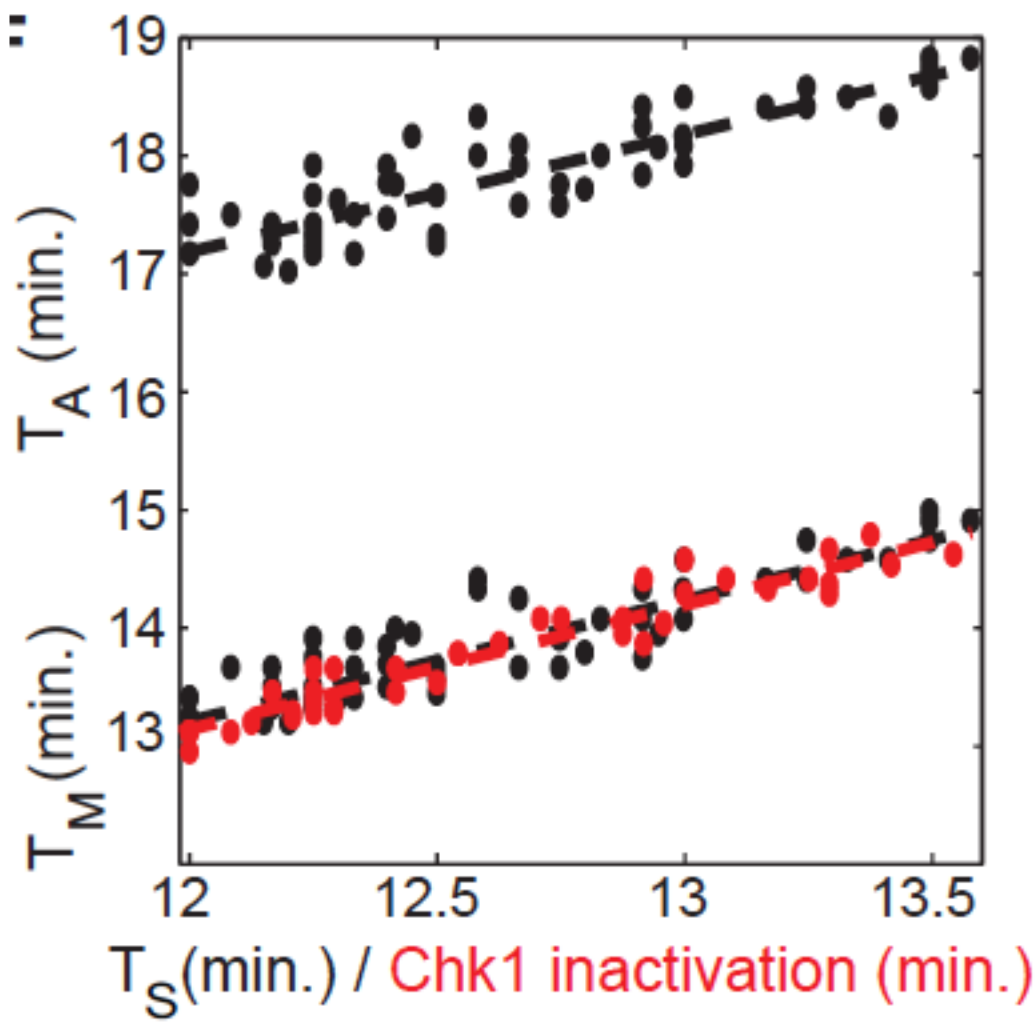
$$d\phi/dt = F(\phi)$$

$$t(\phi_2) - t(\phi_1) = \int_{\phi_1}^{\phi_2} \frac{1}{F(u)}\, du$$

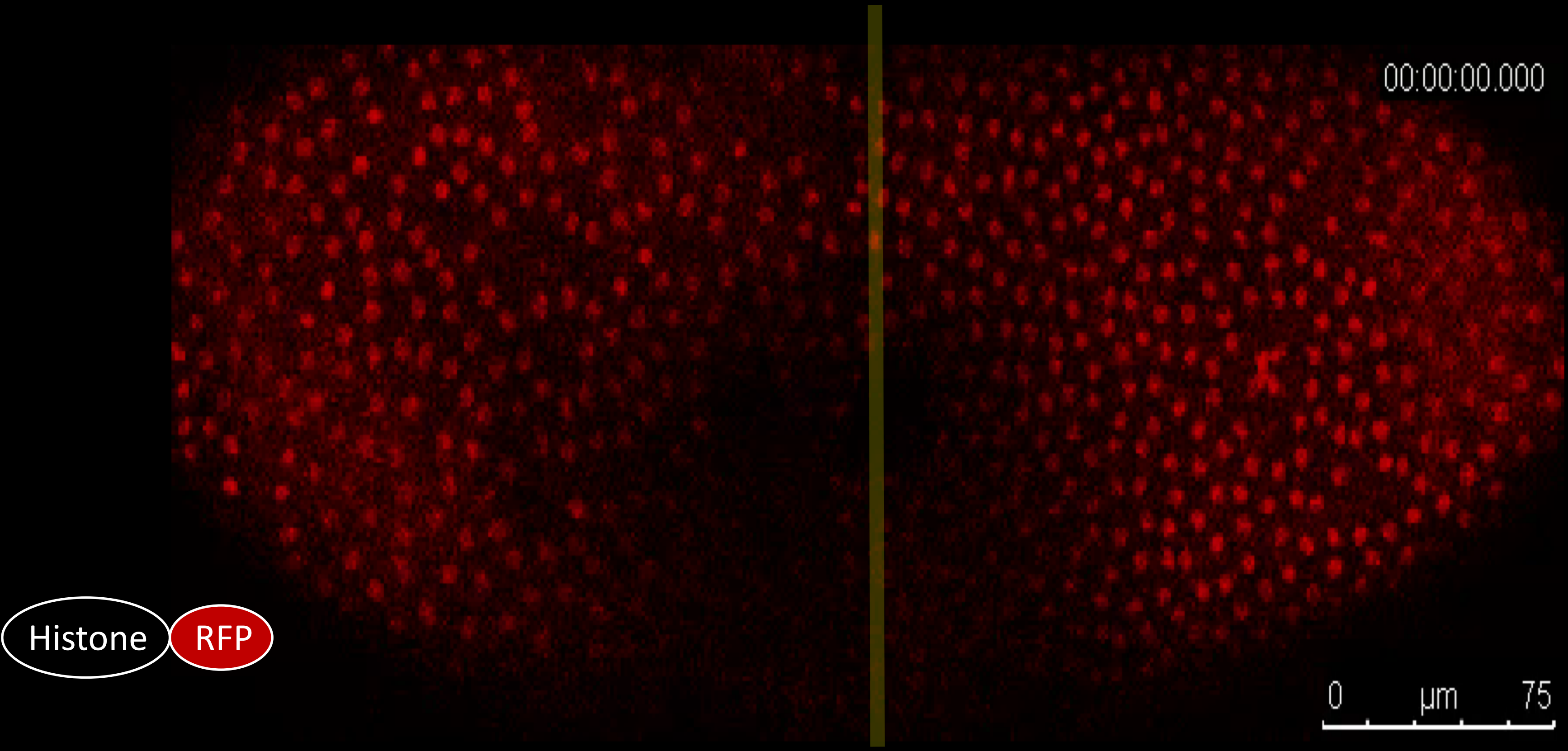


Delays among different points conserved!

Differences in times for completion of S-phase, entry and completion of mitosis are conserved



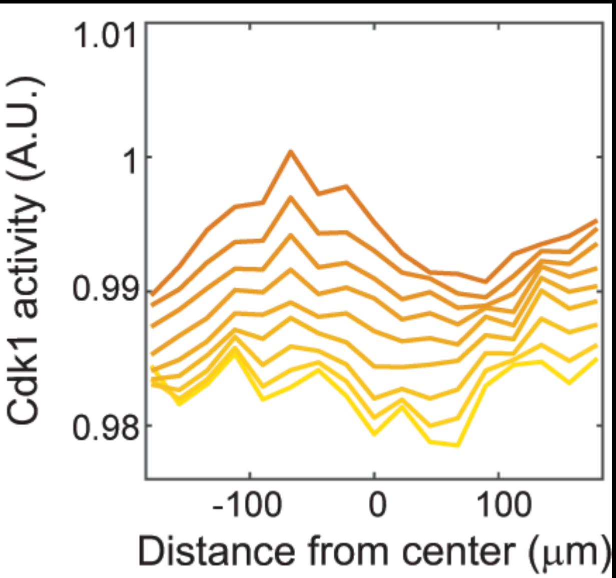
Ligation experiments

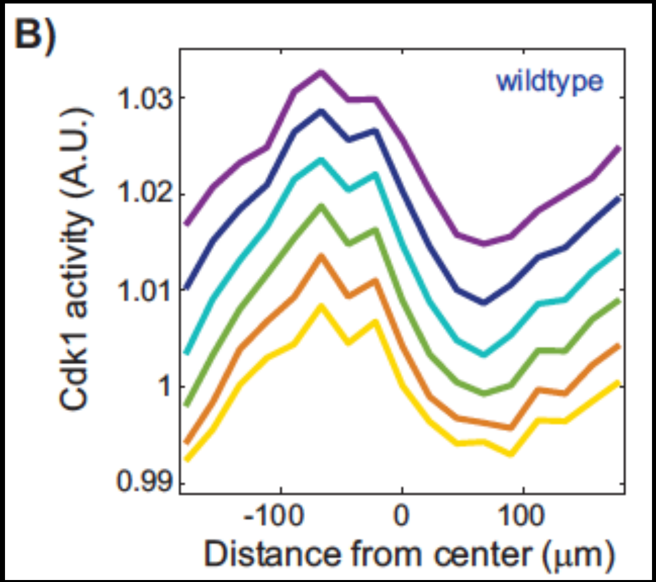


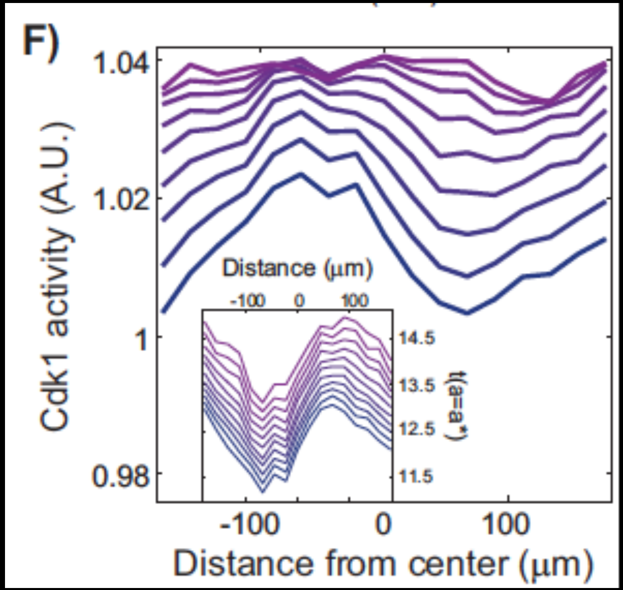
A physical barrier leads to de-synchronization. This was taken as "smoking gun" evidence for trigger waves

Ligation experiments

Sweep vs trigger is not discriminated by ligation experiments in spite of the “phase” nature of the first. Catch: delays are generated by gradients, i.e. a dynamic process







Gradients’ build-up: coupled!

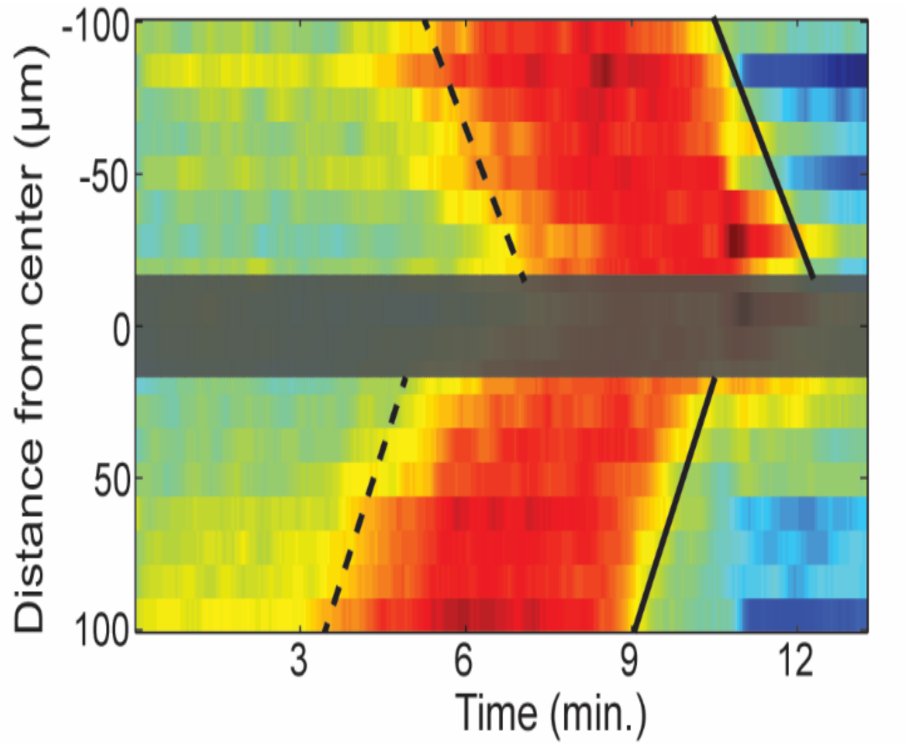
Uncoupled sweep up: gradients undeformed

Uncoupled autonomous growth: gradients deformed, delays preserved

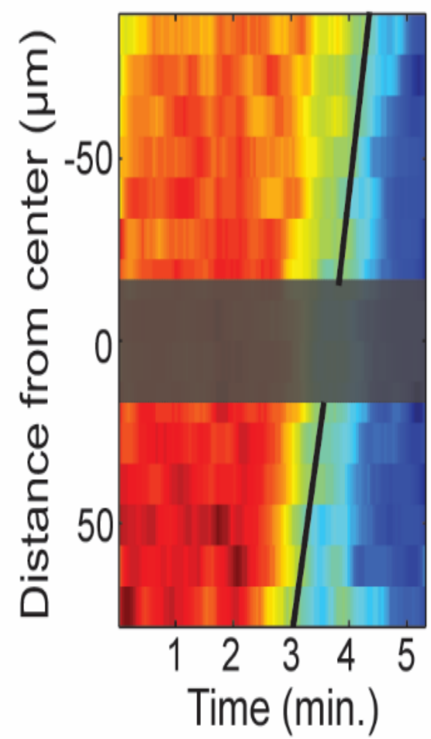
“Timed” ligation experiments

Waves generated in phase II (S-phase) and delays conserved in phase III (mitosis): a barrier inserted in S-phase should disrupt synchronization; no effect during mitosis

S-phase ligation



M-phase ligation



Summary

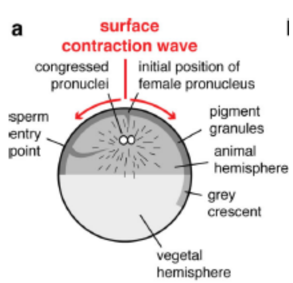
Two regimes for early embryonic waves

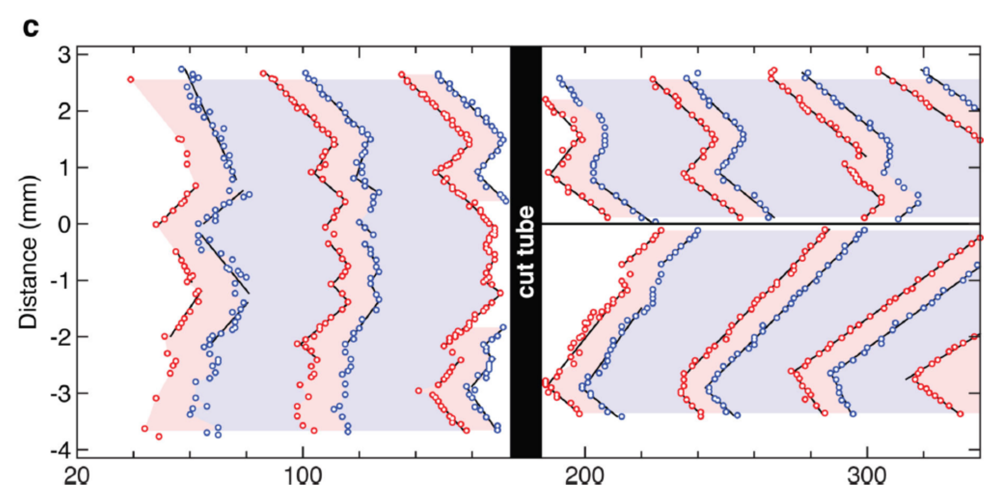
Quasi-adiabatic slow regime. Noise-driven jumps trigger waves of the type known in metastable dynamics.

Fast non-adiabatic regime. The potential changes on time-scales comparable to the spreading, which leads to sweep waves, faster and dependent on parameters differently.

Drosophila WT is in the fast regime. Drive can be slowed down in mutants. Effects of temperature?

Xenopus cell extracts seem to get slower and more regular as cycles proceed. Transition from sweep to trigger?





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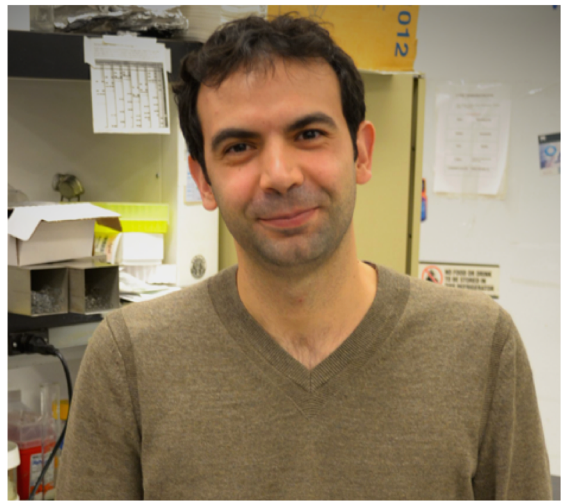

Stefano di Talia

Avaneesh Narla

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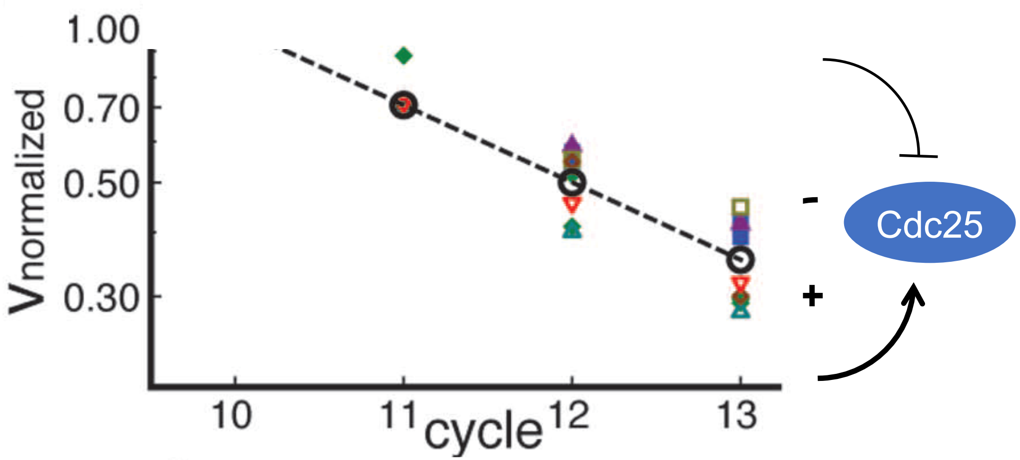
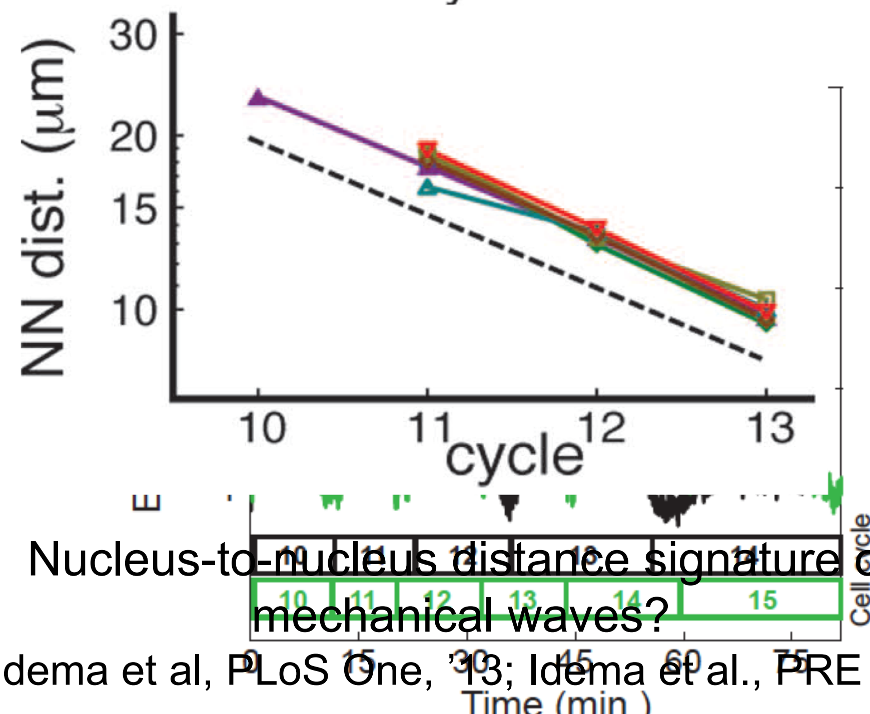
Ruling out mechanical mechanism

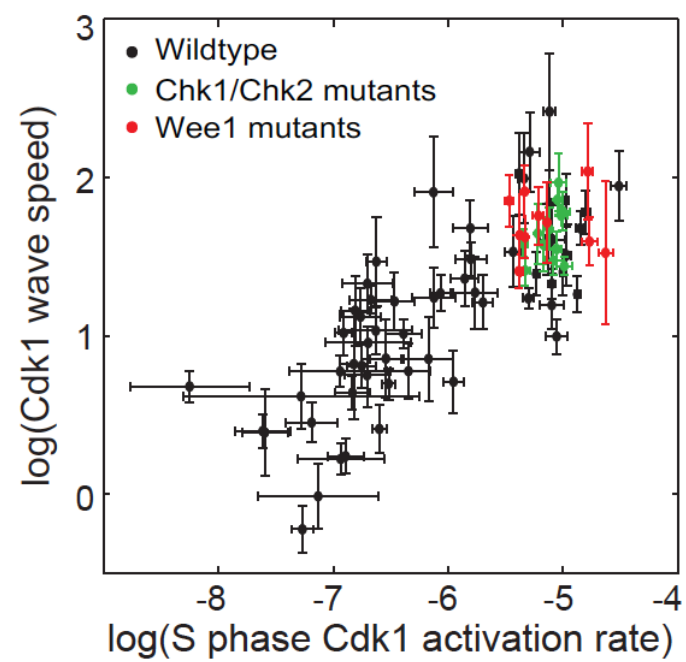


NN distance reduces in these mutants but no slow-down: the wave is not coupled to the # of nuclei

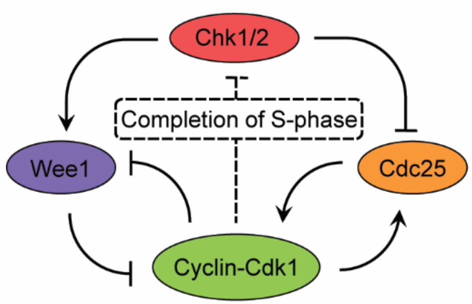


Nucleus-to-nucleus distance signature of mechanical waves?

Idema et al, PLoS One, '13; Idema et al., PRE '14



Reaction-diffusion model recapitulates experimental observations



$$
\begin{aligned}
\frac{\partial f}{\partial t} &= D_{Chk1}\frac{\partial^2 f}{\partial x^2} - \frac{a^\sigma}{K^\sigma_{Chk1} + a^\sigma} r_0 f + \xi_f(x,t) \\
\frac{\partial a}{\partial t} &= D_{Cdk1}\frac{\partial^2 a}{\partial x^2} + \alpha + r_+(a,f)(c(x,t) - a) - r_-(a,f)a + \xi_c(x,t) + \xi_r(x,t) \qquad (1) \\
\frac{\partial c}{\partial t} &= D_{Cdk1}\frac{\partial^2 c}{\partial x^2} + \alpha + \xi_c(x,t)
\end{aligned}
$$

K_{Chk1}= 30 nM

K_{Cdc25}, K_{Wee1}= 40 nM

$$
\begin{aligned}
r_+(a,f) &= \left(c_0 + c_1 \frac{a^\nu}{K^\nu_{Cdc25} + a^\nu}\right)(f_{max} - f) \\
r_-(a,f) &= \left(w_0 + w_1 \frac{K^\mu_{Wee1}}{K^\mu_{Wee1} + a^\mu}\right) f
\end{aligned}
$$

f encodes the effect of Chk1 and its initial level increases as cycles progress