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

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Visualizing the early steps of embryogenesis

HIS-GFP
Imaging nuclear spreading

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Schematics of the very first hours

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

![Graph showing Cdk1/PP1 activity over time and distance from cell cycle](image)
What is the mechanism of these waves and their relation to division waves?

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

\[
\frac{\partial \phi(x,t)}{\partial t} = D \Delta \phi(x,t) + F(\phi)
\]

\[
F(\phi) = -\frac{\partial V}{\partial \phi}
\]

The coupling of diffusion (which brings the field ahead of the front above the barrier) and reactive forces (which bring them upward to the stable point) generates chemical pushed waves.

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 \( \zeta \), 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 I (quasi-adiabatic)

Phase II (sweep waves)

Phase III (delay-preserving)

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

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

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

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

Growth is synchronous

\( (\phi(x) + f(t), \text{ with } f \text{ quadratic}) \): spatial gradients are conserved

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?

\[ \phi^* - gx \]

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

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

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

\[ \zeta_\Phi - F^* \sim F_0 (\beta/F_0^2)^{2/3} \]
Theoretical predictions vs experiments

Dependence on $\beta$ consistent with $7/12$ power (certainly not weak as for bistable)
Theoretical predictions vs model

\[ u \sim \beta^{7/12} D^{3/4} \]

\[ \nu^{1/2} F_0^{5/12} \]

\( \frac{3}{4} \) power in \( D \)

-1/2 power amplitude noise

1/3 power in amplitude
Phase III: rapid autonomous growth

Forces are substantial and their relative change in time is minor.

Growths are largely autonomous:

\[
\frac{d\phi}{dt} = F(\phi)
\]

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

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.
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?
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

\[ \frac{\partial f}{\partial t} = D_{Chk1} \frac{\partial^2 f}{\partial x^2} - \frac{a^\sigma}{K_{Chk1}^\sigma} r_0 f + \xi_f(x,t) \]

\[ \frac{\partial a}{\partial t} = D_{Cdk1} \frac{\partial^2 a}{\partial x^2} + \alpha + r_+(a,f)(c(x,t)-a) - r_-(a,f)a + \xi_c(x,t) + \xi_r(x,t) \]  \hspace{1cm} (1)

\[ \frac{\partial c}{\partial t} = D_{Cdk1} \frac{\partial^2 c}{\partial x^2} + \alpha + \xi_c(x,t) \]

\[ r_+(a,f) = \left( c_0 + c_1 \frac{a^\nu}{K_{Cdc25}^\nu + a^\nu} \right) (f_{max} - f) \]

\[ r_-(a,f) = \left( w_0 + w_1 \frac{K_{Wee1}^{\mu}}{K_{Wee1}^{\mu} + a^\mu} \right) f \]

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

K_{Chk1} = 30 \text{ nM}

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