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Summary

Early embryogenesis is characterized by rapid and synchronous cleavage divisions, which are often controlled by wave-like patterns of Cdk1 activity. Two mechanisms have been proposed for mitotic waves: sweep and trigger waves[1,2]. The two mechanisms give rise to different wave speeds, dependencies on physical and molecular parameters, and spatial profiles of Cdk1 activity: upward sweeping gradients *vs* traveling wavefronts. Both mechanisms hinge on the (transient) bistability of the potential that appears in the reaction-diffusion dynamics governing the progression of the cell cycles across the embryo. The two types of waves are differentiated by the speed of the cell-cycle progression: Sweep/trigger waves arise for rapid/slow drives, respectively. Here, using quantitative imaging of Cdk1 activity and theory, we first illustrate that sweep waves are the dominant mechanism in *Drosophila* embryos, and then test two fundamental predictions on the transition from sweep to trigger waves. Specifically, we demonstrate that sweep waves can be turned into trigger waves if the cell cycle is slowed down genetically or if significant delays in the cell cycle progression are introduced across the embryo by altering nuclear density. Our genetic experiments demonstrate that Polo kinase is a major rate-limiting regulator of the timing of blastoderm divisions and is highly effective at inducing the sweep to trigger transitions. Furthermore, we test the effects of temperature on cell cycle timing and mitotic waves. We show that changes in temperature cause an essentially uniform slowdown of interphase and mitosis. That results in sweep waves still being observed across a wide temperature range in spite of the cell cycle durations being significantly longer. Collectively, our combination of theory and quantitative imaging elucidates the nature of mitotic waves in *Drosophila* embryogenesis, their control mechanisms and their mutual transitions.

Results

Sweep and trigger waves are characterized by different dynamical and physical properties

In most metazoans, early embryogenesis begins with a series of rapid and synchronous cleavage divisions, which ensures a swift increase in the number of cells prior to morphogenesis[3]. In many species, the coordination of these cleavage divisions is characterized by mitotic waves[4]. The *Drosophila* embryo provides an ideal system for the elucidation of the physical and molecular mechanisms of these waves, as the major biochemical activities controlling these waves can be visualized and quantified *in vivo* by using biosensors[5].

In the *Drosophila* embryo, mitotic waves arise from the reaction-diffusion dynamics of Cdk1. In *Drosophila* syncytium, active Cdk1 complexes can diffuse in the cytoplasm enclosing multiple nuclei. Moreover, Cdk1 is characterized by a transient bistability, i.e., the potential in the reaction-diffusion dynamics is bistable during the S-phase of the cell cycle and transitions to a monostable shape by the beginning of mitosis. The coupling of diffusion and bistability can result in the generation of traveling waves[6,7]. Recently, we used imaging experiments to characterize existence and properties of these waves[2,5]. Using a FRET biosensor for the activity of the mitotic kinase Cdk1, we showed that mitotic waves in *Drosophila* embryos are indeed controlled by Cdk1 waves[5] compatible with sweep waves, a new type of reaction-diffusion mechanism for the generation of wave-like spreading[2].

Two mechanisms have been proposed for Cdk1 waves: sweep and trigger waves. Sweep waves arise when the cell cycle is driven rapidly, while trigger waves are observed when cell-cycle progression is slow. The reason explained here is intuited from Figure 1 (see Ref. 2 for full details), which visually conveys the mathematical formulation of the dynamics as a reaction-diffusion

system. During the initial period of bistability, the rate of change of Cdk1 activity represented in Figs. 1A, B has three zeros (two stable fixed points and one unstable). The two stable points correspond to low (interphase) and high (mitosis) Cdk1 activity. Stability of these states can be further understood by observing that the rate of change of Cdk1 activity can be derived from an effective potential energy function. Such potential is shown in Fig. 1C and has two minima, the lowest one at high values of Cdk1 activity being the most favorable state, and the minimum at low value of Cdk1 activity being metastable. Trigger waves can arise when regions in the most favorable state, i.e., high Cdk1 activity, are in proximity with regions in the metastable state, i.e., low Cdk1 activity. In this scenario, diffusion of active Cdk1 complexes can trigger the transition from low to high activity as shown in Fig. 1C and leads to a traveling wavefront of Cdk1 activity. Trigger waves have a characteristic velocity which is essentially insensitive to noise and to the rate at which the system transitions from the bistable to the monostable regime. However, the initiation of trigger waves is expected to be sensitive to noise, as noise can produce the jump from the low to the high Cdk1-activity state. These considerations indicate why the transition from the bistable to the monostable state should not be fast for trigger waves to appear. Indeed, a slow transition ensures enough time for the noise to seed a wave (by crossing the "energy" barrier shown in Figure 1C) and for the wave to spread. To illustrate this last point, let us imagine what Cdk1 trigger waves would be like in *Drosophila* embryos. Mathematical modeling and genetic mutants suggest that the speed of such waves is about 0.4 μm/s. Thus, trigger waves would require about 10 minutes to travel half of the embryo length. However, since the cell cycle is very rapid (lasting 8-18 minutes at different nuclear cycles) and all nuclei divide within less than 2 minutes throughout early embryogenesis, most nuclei would have spontaneously transitioned to mitosis prior to the time

when the wavefront would reach them. These arguments suggest that trigger waves are unlikely to be the mechanism that can ensure a coupling among nuclei in *Drosophila* embryos.

Let us now consider what happens when the cell cycle is driven rapidly. In this scenario, all regions of the embryo would transition from the bistable to the monostable regime around the same time and prior to the creation (or significant spreading) of a trigger wave. At that point, the system enters the region around the saddle-node bifurcation (see Fig. 1D). There, the force is close to zero and its time-dependency is important. Furthermore, being close to a minimum, spatial dependencies of the force are much tamed. How does wave-like spreading arise? The reason is that the Cdk1 field at the time of loss of bistability is not uniform and the time-dependent force is spatially roughly uniform. Due to noise (and spatial variations in nuclear density and/or other relevant biological quantities), the Cdk1 field is stochastic. Both theoretical and experimental results indicate that the stochastic Cdk1 fields in interphase have a correlation length of about 100-150 microns. This relatively substantial length makes that diffusion plays a minor role and the dynamics is dominated by the action of the force in Figure 1D. Thus, sweep waves arise because spatially inhomogeneous fields of Cdk1 activity formed during interphase respond to a spatially constant force (Figure 1D) and move up at a uniform rate across the entire embryo as nuclei transition towards high Cdk1 activity (Figure 1F). The third phase of the dynamics when the Cdk1 field is distorted but the delay imposed by the sweep wave are preserved is not essential here and we refer to Ref. 2. Collectively, these arguments indicate that mitotic waves in *Drosophila* are phase waves (diffusion not being involved), but that the early phase when Cdk1 activity gradients form requires physical coupling via diffusion. Consistently, experiments inserting physical barriers in the embryos found that mitotic waves can be decoupled only if nuclei are physically separated

in early to mid S-phase, but that the following interphase waves behave as phase waves. Another consequence of the drastically different dynamical processes underlying the two types of waves is that sweep waves have different dependencies from physical parameters like noise, diffusivity, etc., than trigger waves (see Ref.2). In particular, changing the rate at which the system transitions from bistability to monostability impacts how quickly gradients move up and thus has a significant impact on the speed of sweep waves. On the contrary, the speed of trigger waves has a very weak (logarithmic) dependency on the rate. Noise influences the formation of the Cdk1 gradients in interphase and thus also has a significant impact on the speed of sweep waves, but it can be shown that its impact on the speed of trigger waves is negligible.

The arguments outlined above predict that decreasing the rate at which the cell cycle is driven would trigger a transition from sweep to trigger waves. Moreover, a central feature of sweep waves is that bistability is lost synchronously across the embryo. Different dynamics are expected when there are significant delays in the progression of the cell cycle across the embryo. Here, we set out to test the previous theoretical predictions, which allow us to establish two determinants of the nature of embryonic waves: 1. The speed of the cell-cycle drive; 2. The synchronicity of cell-cycle progression across the embryo. To this end, we used both physical (temperature) and genetic perturbations to alter both the cell cycle dynamics and the positioning of nuclei so as to manipulate the time when nuclei transition from a bistable to a monostable region of Cdk1 activity.

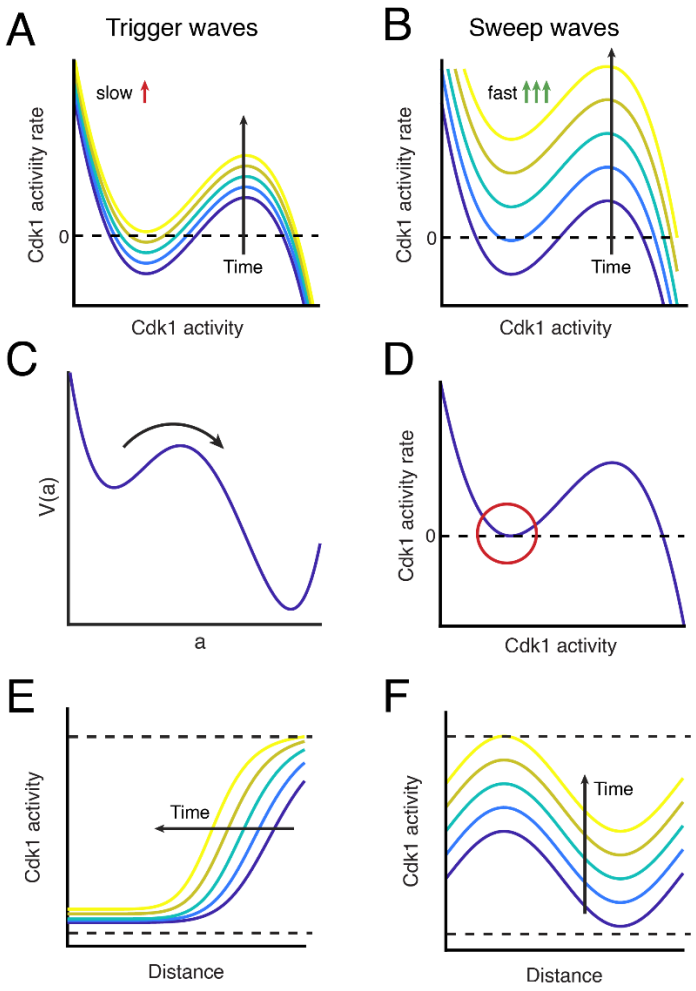

Figure 1 Trigger vs sweep waves in transient bistable systems. A sketch of transiently bistable systems driven slowly (**A**) or rapidly (**B**). **C)** Illustration of the energy potential controlling the behavior of trigger waves. In the case when the drive is slow, the spatial spreading of activity happens at a time when the system is metastable. The wave is driven by a jump across the potential barrier that separates the metastable from the stable point. Its spreading requires a nucleation step, as an energy barrier must be crossed as shown in the cartoon. **D)** Illustration of Cdk1 activity rate around the time of the onset of sweep waves. In the case when the drive is fast, bistability is lost uniformly across the embryo and activity in the entire embryo is driven by the dynamics near the saddle-node bifurcation where bistability is lost (red circle). As a result, activity increases at the same rate across the embryo, thus preserving pre-existing gradients established by the early dynamics. Prediction for the temporal evolution of Cdk1 spatial profile in the case of slow (**E**) and fast (**F**) drives. Notice that the slow case is characterized by a traveling wavefront (trigger waves) while the fast case is characterized by conserved gradients that move overall up as time progresses (sweep waves). See also Figure S1.

Sweep waves are observed across a large range of temperatures

To test the above arguments, we sought to identify physical and/or genetic manipulations that would affect the transition from interphase to mitosis. To this end, we first tested the effects of lowering the temperature at which embryos develop[9]. We envisioned two possible scenarios: lowering the temperature could either cause a differential slowdown among cell cycle processes or it could be equivalent to a global rescaling of time. In the first scenario, the ratio of timescales involved in the control of the waves could be affected. Alternatively, a global rescaling of time would not alter ratios of timescales and the nature of the waves. To distinguish between these two scenarios, we developed a setup for precise control of the temperature at which embryos develop under the microscope (Figure 2A). Using this setup, we generated a range of temperature (14-25 °C) for embryonic development (Figure S2D). We found that the duration of cell cycle 13 significantly increases as the temperature is lowered, from about 18 minutes at 25 °C to about 60 minutes at 14 °C (Figure 2B). The lengthening of the cell cycle is accompanied by a slowdown of mitotic waves, although the relationship between the two quantities is noisy (Figure 2C). Most importantly, analysis of the spatial properties of the Cdk1 activity field revealed that, even when the temperature is lowered, the activity is still characterized by sweep waves rather than a wavefront (Figure 2D-2F and Figure S2). These observations suggest that changing temperature does not change the properties of the mitotic waves, which remain sweep across the temperature range tested. Consistently with this interpretation, we found that the dynamics Cdk1 activity at different temperatures can be perfectly rescaled using a single scaling factor (Figure 2G-2I). Thus, we conclude that temperature causes a global slowdown of the cell cycle, which does not alter the nature of mitotic waves.

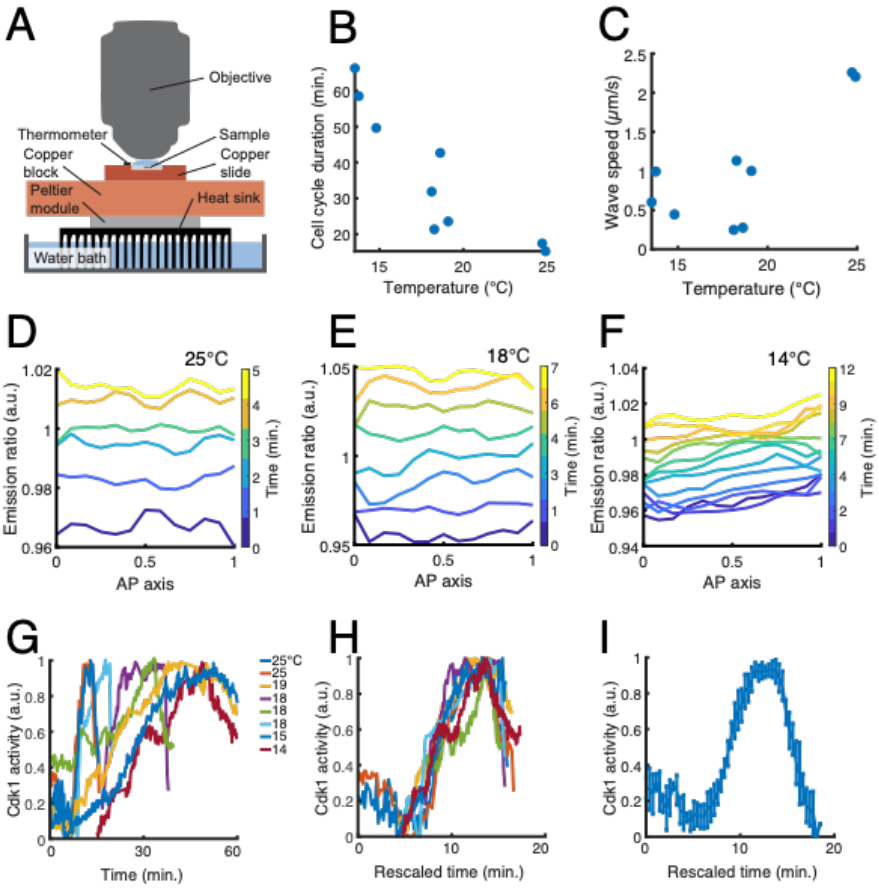

Figure 2. Effects of temperature on mitotic waves. A) Setup to change the temperature at which embryos develop. **B)** The duration of cell cycle 13 as a function of temperature. **C)** The speed of mitotic waves as a function of temperature. Cdk1 activity as a function of space at different times for embryos developing at 25 °C (**D**), 18 °C (**E**) and 14 °C (**F**). **G)** Time profiles of Cdk1 activity at different temperatures. **H)** Cdk1 activity rescaled by normalizing time relatively to 25 °C. **I)** Average renormalized Cdk1 activity (error bars: s.e.m.). See also Figure S2.

Trigger waves in *polo* heterozygous embryos.

Since changing temperature did not alter the properties of mitotic waves, we tested whether such properties can be altered by using genetic perturbations. Specifically, we tested whether changing the activity of major regulators of the cell cycle[10] could change ratios of time scales so as to cause a transition from sweep to trigger waves. The cell cycle is driven by a gradual increase of Cdk1 activity in S-phase until sufficient activity is reached to trigger rapid increase of Cdk1 activity (via positive feedbacks) and mitotic entry[10]. The synthesis of rate-limiting regulators of the cell cycle,

e.g. mitotic cyclins, contribute to the rate at which the embryo transition from S to M-phase and thus contribute to set the rate at which bistability is lost. We had previously used cyclin A and cyclin B heterozygous and shown that, while they cause a slowdown of the cell cycle and a consequent reduction in Cdk1 wave speed, this change could still be explained by sweep waves[2]. We confirmed this observation by analyzing the spatial profiles of Cdk1 activity and finding that they are described by sweeping gradients. Thus, we sought to find other genetic perturbations which might result in a transition from sweep to trigger waves. Specifically, we focused on the role of Polo kinase, an important regulator of mitosis, which operates in several feedback mechanisms with Cdk1 to drive mitosis[11,12]. First, we measured cell cycle duration in *polo* heterozygous embryos. We found that the duration of cell cycle 13 is significantly increased compared to both wild type and cyclin A/B heterozygous (Figure 3A). It is also clear from Fig. 3A that the slowdown is not a global rescaling of time, though. Indeed, the initial phase is slower while the rate of increase around the entry in mitosis is comparable to the wild type. Thus, we tested whether the Cdk1 waves are indeed trigger waves in at least some of the *polo* heterozygous embryos We found that in 3 out of 9 embryos the spatial profiles of Cdk1 activity are inconsistent with sweep waves and consistent with dynamic traveling wavefronts (Figure 3D and S3). These embryos correspond to the ones with the slowest wave-like propagation and the longest cell cycles, suggesting that the slowdown of the cell cycle in this mutant is sufficient to posit embryos near the transition from trigger to sweep waves[2]. As a result, a fraction of embryos has trigger rather than sweep waves. Moreover, the speed of the waves in those embryos was about 0.3-0.4 μm/s, which is compatible with the speed observed in other genetic mutants previously shown to feature traveling bistable wavefronts[2]. This speed is also consistent with the prediction of a mathematical model able to capture the essential properties of the mitotic waves[2]. Thus, we conclude that in

some *polo* heterozygous embryos the cell cycle is significantly slower to result in trigger rather than sweep waves, confirming a fundamental prediction of our theory. Note finally that our results show that Polo plays a significant rate-limiting role in timing the cell cycle of early *Drosophila* embryos.

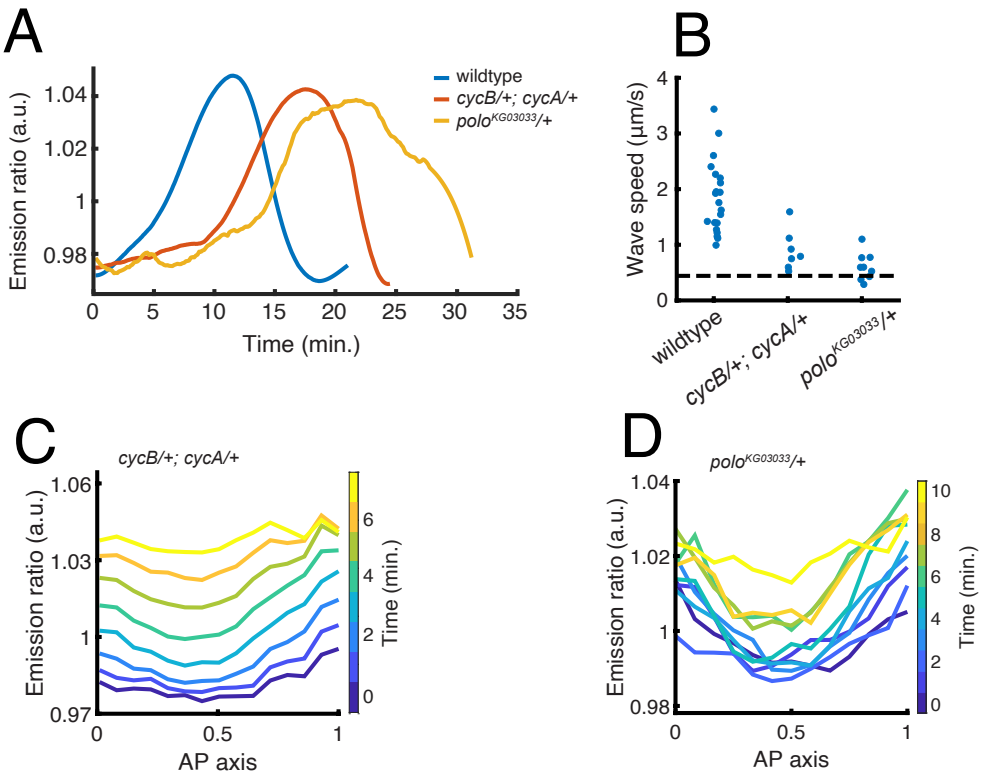

Figure 3 Mitotic waves in cyclins and *polo* heterozygous mutants. A) Average Cdk1 activity over time for wild type, cyclins and *polo* heterozygous. **B)** Wave speed for the different genotypes. Dotted line indicates the maximum speed for a trigger wave predicted by our model. Spatial profiles of Cdk1 activity in cyclins heterozygous (**C**) and *polo* heterozygous (**D**) mutant embryos. See also Figure S3.

Trigger waves in embryos with gradients of nuclear density

An additional prediction of the arguments laid down above goes as follows. Suppose that the progressions of the cell cycle among different regions of the embryos are delayed with respect to each other. Then, some regions would be in the monostable regime at high values of Cdk1 (see Fig. 1) while other regions would still be in the metastable state at low activities of Cdk1. In this

case, one would expect that regions at high Cdk1 activity would invade metastable regions by spreading fronts akin to trigger waves rather than sweep waves. In other words, by having significant delays of the cell cycle across the embryo, we bypass the need for the jumps in Fig. 1C and therefore directly access the trigger waves regime.

To generate the above conditions of substantial delays in the progression of the cell cycle, we reasoned that its regulation is strongly linked to the activation of the DNA replication checkpoint which in turn is controlled by the nuclear-to-cytoplasmic ratio[4,13]. Therefore, mutants that alter nuclear positioning could in fact result in conditions with substantial delays. Consistently with this idea, we found in numerical simulations of a mathematical model for Cdk1 activity[2,5] that the presence of a gradient of nuclear density/Chk1 activity leads to trigger waves *in lieu* of sweep waves. Consistently with the observed wave being a trigger wave, we found that the speed of the wavefront coincides with that predicted theoretically[7] for a trigger wave. Next, we set out to test this prediction of the mathematical model with experiments. To this end, we used *cul-5* mutant embryos which display a nuclear density gradient across the anterior-posterior axis[14]. We found that in some of these embryos, Cdk1 waves are characterized by a traveling wavefront rather that increasing gradients (Figure 4G and S4). Moreover, the speed of the waves (0.4 μm/s) is much slower than what is observed in wild type, and it is consistent with the speed observed in *polo* heterozygous and expected for a trigger wave[2]. Thus, we conclude that introducing significant delays in cell cycle timing by changing nuclear density can result in trigger rather than sweep waves. Collectively, these observations and previous observations on *polo* heterozygous mutants confirm that mitotic waves in *Drosophila* are sweep waves and that both rapid and synchronous regulation of Cdk1 activity is needed for such waves.

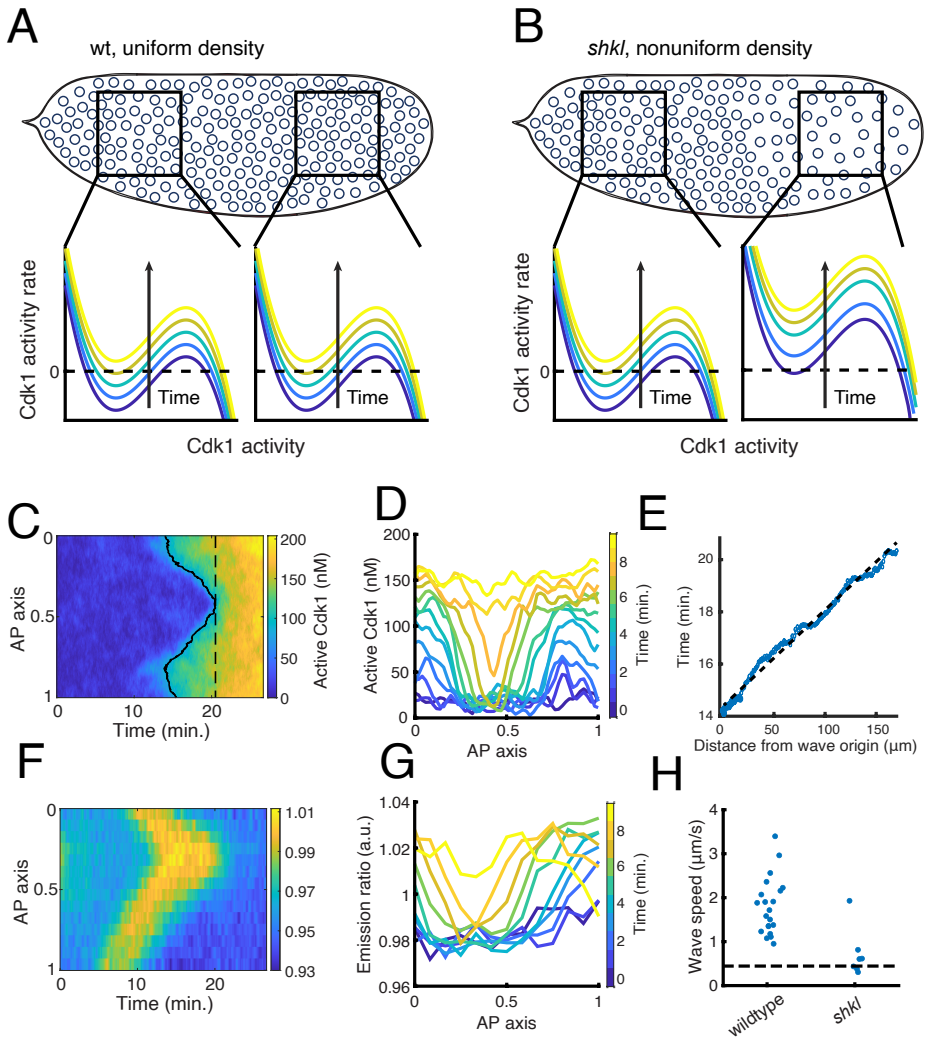

Figure 4 Mitotic waves in mutants displaying defects in nuclear positioning. Cartoons representing nuclear density and Cdk1 control in wild type (A) vs shkl embryos (B). **C)** Heatmap of Cdk1 activity from a numerical simulation of an embryo having nuclear density gradients. The dotted black line indicates the time when bistability is lost. (**D**) Spatial profiles of Cdk1 activity as a function of time predicted by our model. **E)** Time at which Cdk1 activity passes a threshold as a function of distance from the wave origin. The plot shows a wave-like spreading with the speed predicted for a trigger wave (dotted line). Heatmap **(F)** and spatial profiles of Cdk1 activity **(G)** in a *shkl* embryo. (**H**) Wave speed in wild type vs *shkl* embryos. The dotted line indicates the maximum speed of trigger waves predicted by our model. See also Figure S4.

Discussion

Mitotic waves are ubiquitous in embryonic development and ensure that nuclear/cell divisions are synchronized across the large expanse of the embryo[1,2,5,15-18]. Two main mechanisms have been

described for mitotic waves in early embryos: trigger and sweep waves[6]. Trigger waves represent a classic and well-studied mechanism by which a stable region can invade a metastable one and several important features of these waves have been derived in the literature[7]. Sweep waves were recently described by our group to understand the different properties of Cdk1 waves in early *Drosophila* embryos, namely the existence of sweeping gradients rather than traveling wavefronts of Cdk1 activity[2].

Here, we showed that the nature of mitotic waves in *Drosophila* embryos can be manipulated by using two fundamental elements of sweep waves: rapid loss of bistability and synchronicity of such loss across the embryos. In the absence of either one of these two features, trigger waves should be observed instead of sweep waves. Both predictions were confirmed.

The genetic perturbations used here have interesting implications for our understanding of the embryonic cycles. We found that Polo kinase is a major rate-limiting regulator of the embryonic cycles, and its effects are reflected in altered Cdk1 activity. Our observations reinforce the importance of the multiple regulatory feedbacks that ensure mutual control between Polo and Cdk1[19]. We have previously shown that nuclear positioning is crucial for the synchronicity of mitosis prior to the maternal-to-zygotic transition[20]. Since nuclear density (N/C ratio) influences cell cycle duration, altered nuclear positioning results in gradients of nuclear density which in turn could explain the significant mitotic delays. However, one might have expected that, once a mitotic wave is initiated, such wave could quickly travel across the embryo and equalize the delays imposed by different nuclear densities across the embryo. In fact, waves in wild type embryos at cycle 13 usually take only 2 minutes to travel across the entire embryo. Our results explain why mitotic waves are unable to give a rapid synchronization of the cell cycle when nuclear positioning is significantly altered: since waves are trigger rather than sweep, they are significantly slower and

take longer to spread over the entire embryo. Notably, since *cul-5* seems to only impact the cell cycle indirectly by impacting the nuclear-to-cytoplasmic ratio[14], these experiments essentially allow us to infer what the speed of a trigger wave at cell cycle 13 would be. This speed is about 5-fold lower than that observed in wild type, further confirming the ability of sweep waves to travel across the embryo much faster.

In conclusion, signaling waves are emerging as a general mechanism of regulation of developmental processes[6,21-23]. Our work stresses the importance of a solid interplay between theory and experiments, directly visualizing biochemical waves and their properties, to identify convincingly the mechanisms that control wave propagation in complex biological systems.

Acknowledgments

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Author contributions

Conceptualization, L.H., M.V., and S.D.; Methodology, L.H., W.H., and S.D.; Software, L.H., and S.D.; Investigation, L.H., W.H., M.V., and S.D.; Writing – Original Draft, M.V. and S.D.; Supervision, M.V. and S.D.; Funding Acquisition, M.V. and S.D.

Declaration of interests

The authors declare no competing interests.

STAR Methods

RESOURCE AVAILABILITY

Lead Contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Stefano Di Talia (stefano.ditalia@duke.edu).

Materials Availability

Newly generated fly lines in this study have not been deposited to a central repository but are available without restriction from the lead contact.

Data and Code Availability

- All original code has been deposited at Github at the following link and is publicly available as of the date of publication: https://github.com/lhaydene26/Hayden_MitoticWaves2022
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Fly Lines and Husbandry

For all experiments, adult male and female flies of *Drosophila melanogaster* were raised at room temperature (~22°C) on standard molasses food without light/dark cycle. Prior to embryo collection, adult flies were moved to a 25°C incubator without light/dark cycle for a minimum of 2 days. Embryos were collected on apple juice agar plates with yeast paste from containers containing both male and female flies. Experiments in this study used embryos from cc 13 to cc

14 at ~2h of age, determined by examining nuclear numbers and movement. The fly lines used or generated in this study are described in the Key Resources Table.

METHOD DETAILS

Embryo Processing

After collection, embryos were dechorionated with 50% bleach for 1 minute, rinsed twice with water, placed in halocarbon oil on a gas-permeable membrane, and covered with a glass coverslip.

Temperature control

To control the temperature of the embryo, we used a Peltier module to cool a copper plate on which the sample was mounted. The hot side of the Peltier module sat on an aluminum heat sink immersed in a cold-water bath. The water bath was refreshed regularly by adding small amounts of ice and removing water as needed. We used an Arduino Uno microcontroller to monitor a thermometer adjacent to the sample and regulate power to the Peliter module as needed to control temperature.

Microscopy

Images were acquired through confocal microcopy using a Leica SP8 confocal microscope and its software, Leica Application Suite X, using a 20x/0.75 numerical aperture air objective, an argon ion laser and a 561nm diode laser.

QUANTIFICATION AND STATISTICAL ANALYSIS

Image Analysis

All image analysis steps were performed using custom-written MATLAB algorithms unless otherwise noted. Confocal images were exported as .tif files from LAS AF software for use in MATLAB algorithms.

Quantification of Cdk1 Biosensor

Cdk1 FRET curves were computed by taking the fluorescence intensity ratio of YFP signal over CFP signal (the emission ratio). To correct for slight out-of-focus shifting and embryo drift, the data were normalized and detrended. This signal was averaged over the entire embryo cortex in Figure 3A and in rectangles of width 22.4μm when quantifying Cdk1 activity across the AP axis.

Quantification of Mitotic Wave Speed

Mitotic wave speed was calculated by measuring the location of the wavefront as a function of time in a histone-RFP channel, beginning with the time point when metaphase began in the posterior of the embryo.

Mathematical Modeling

We modified a mathematical model of Cdk1 activity[2] to introduce gradients of nuclear density across the Anterior-Posterior axis. The model reads:

$$\frac{\partial a(x,t)}{\partial t} = D\nabla^2 a(x,t) + G(a,t) + \eta(x,t)$$

where

$$G(a,t) = G_0[\alpha + r_+(a)(c(t) - a) - r_-(a)a]$$

and

$$r_+(a) = \left(c_0 + c_1 \frac{a^n}{K_{Cdc25}^n + a^n}\right)\left(1 - h_0(x)\frac{K_{Chk1}^s}{K_{Chk1}^s + a^s}\right)$$

$$r_-(a) = h_0(x)\left(w_0 + w_1 \frac{K_{Wee1}^n}{K_{Wee1}^n + a^n}\frac{K_{Chk1}^s}{K_{Chk1}^s + a^s}\right)$$

The quantity $c(t) = \alpha t$ denotes the total amount of Cyclin-Cdk1 complexes, so that the difference $c(t) - a(x,t)$ reflects the amount of inactive Cdk1. The first term in $r_+(a)$ describes the positive feedback between Cdk1 and Cdc25, the second term the negative regulation of Cdc25 by Chk1 and the negative feedback of Cdk1 on Chk1. The $r_-(a)$ describes the double negative feedback between Cdk1 and Wee1, the modulation of Wee1 activity by Chk1 and the negative feedback of Cdk1 on Chk1. Note that our model focuses on the activation of Cdk1 and does not explicitly model its inactivation at the exit from mitosis. The rationale is that we have previously shown that the exit from mitosis is controlled by a phase wave that reflects the delays set by the earlier Cdk1 wave, which times the entry into mitosis[24]. The noise term is a Langevin, Gaussian noise with short spatiotemporal correlations:

$$\langle \eta(x,t)\eta(x',t')\rangle = \sigma^2 G_0[\alpha + r_+(a)(c(t)-a) + r_-(a)a]\delta(x-x')\delta(t-t')$$

Gradients of nuclear density from the poles (with a typically lower density at the posterior, as experimentally observed[14,25]) were introduced by defining $h_0(x)$ as the sum of two gaussians:

$$h_0(x) = h_0 - h_1 e^{-\frac{x^2}{2\lambda^2}} - h_2 e^{-\frac{(L-x)^2}{2\lambda^2}}$$

where x is the position along the Anterior-Posterior Axis ($x = 0$ at the Anterior pole and $x = L$ at the Posterior pole). The stochastic model was simulated using finite differences and Euler method with reflecting boundary conditions.

The maximum speed of trigger waves compatible with the model was computed using the standard method described previously[7,26]. Specifically, we computed $G(a,\bar{t})$ at a time $\bar{t}$ that precedes by a few seconds loss of bistability. We then simulated the movement of a particle of mass D subject to a force $-G(a,\bar{t})$ and friction coefficient v. The speed of the wave v was identified as the smallest value of the friction coefficient for which the particle did not cross the lowest peak of the inverted potential[7,26].

KEY RESOURCE TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, peptides, and recombinant proteins		
Halocarbon Oil 27	Sigma	Cat # 9002-83-9
Experimental models: Organisms/strains		
D. melanogaster: w; Cdk1-FRET; His2Av-mRFP	S. Di Talia[5]	N/A
D. melanogaster: w;; shkl^{GM130}/TM3	R. Lehmann[24]	N/A
D. melanogaster: w;; shkl^{GM163}/TM3	R. Lehmann[24]	N/A
D. melanogaster: w[*]; CycB[2]/CyO, P{ry[+t7.2]=ftz-lacB}E3	Bloomington Drosophila Stock Center	BDSC: 6630; FlyBase: FBst0006630
D. melanogaster: w[*]; CycA[C8LR1]/TM3, Sb[1] P{w[+mC]=35UZ}2	Bloomington Drosophila Stock Center	BDSC: 6627; FlyBase: FBst0006627
D. melanogaster: y[1]; P{y[+mDint2] w[BR.E.BR]=SUPor-P}polo[KG03033] ry[506]/TM3, Sb[1] Ser[1]	Bloomington Drosophila Stock Center	BDSC: 13941; FlyBase: FBst0013941
Software and algorithms		
MATLAB R2020a	Mathworks	N/A

Table S1. Parameters of the model

Parameters	Values
D	$5\mu m^2\ s^{-1}$
K_{Chk1}	48 nM
K_{Cdc25}	39.6 nM
K_{Wee1}	39.6 nM
A	8 nM min^{-1}
c_0	0.12 min^{-1}
c_1	0.65 min^{-1}
w_0	0.24 min^{-1}
w_1	1 min^{-1}
N	5
S	10
t_0	20.3 min
σ	11 $nM^{1/2}\mu m^{1/2}$
h_0	0.65
h_1	0.15
h_2	0.3
L	512 μm
λ	53 μm
Γ	0.05

Supplementary Figures

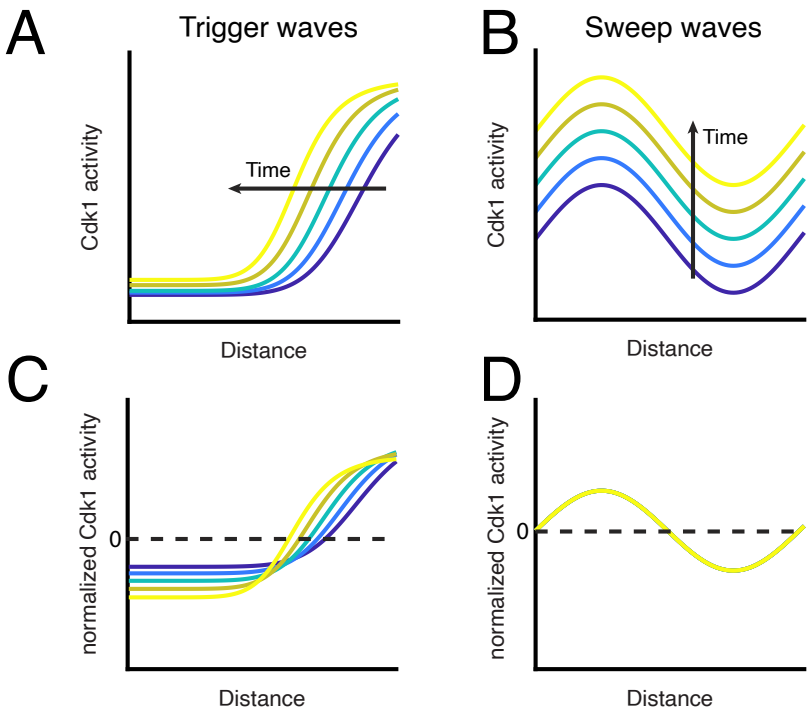

Figure S1. Rescaling of trigger and sweep waves. Temporal evolution of Cdk1 spatial profiles in the case of slow (A) and fast (B) drives, as in Figure 1. (C, D) Spatial profiles rescaled by subtracting their mean Cdk1 activity in trigger (C) and sweep (D) waves. Because trigger waves are characterized by a traveling wavefront, spatial curves remain separate, while in sweep waves where gradients move uniformly upwards with time, all curves collapse together.

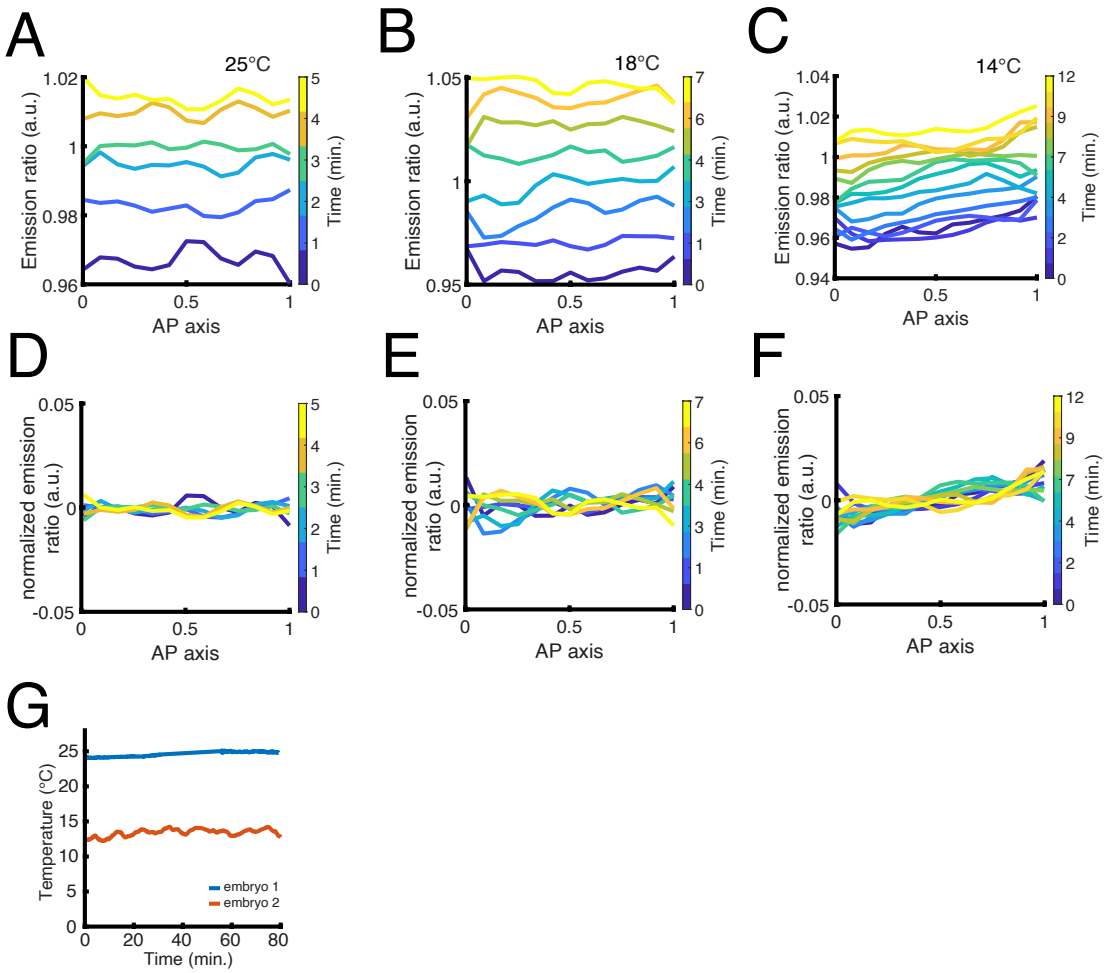

Figure S2. Temperature control and wave rescaling. Spatial profiles of normal (A-C) and rescaled (D-F) Cdk1 activities at 25 °C (A, D), 18 °C (B, E), and 14 °C (C, F). G) Temperature timeseries for two representative samples.

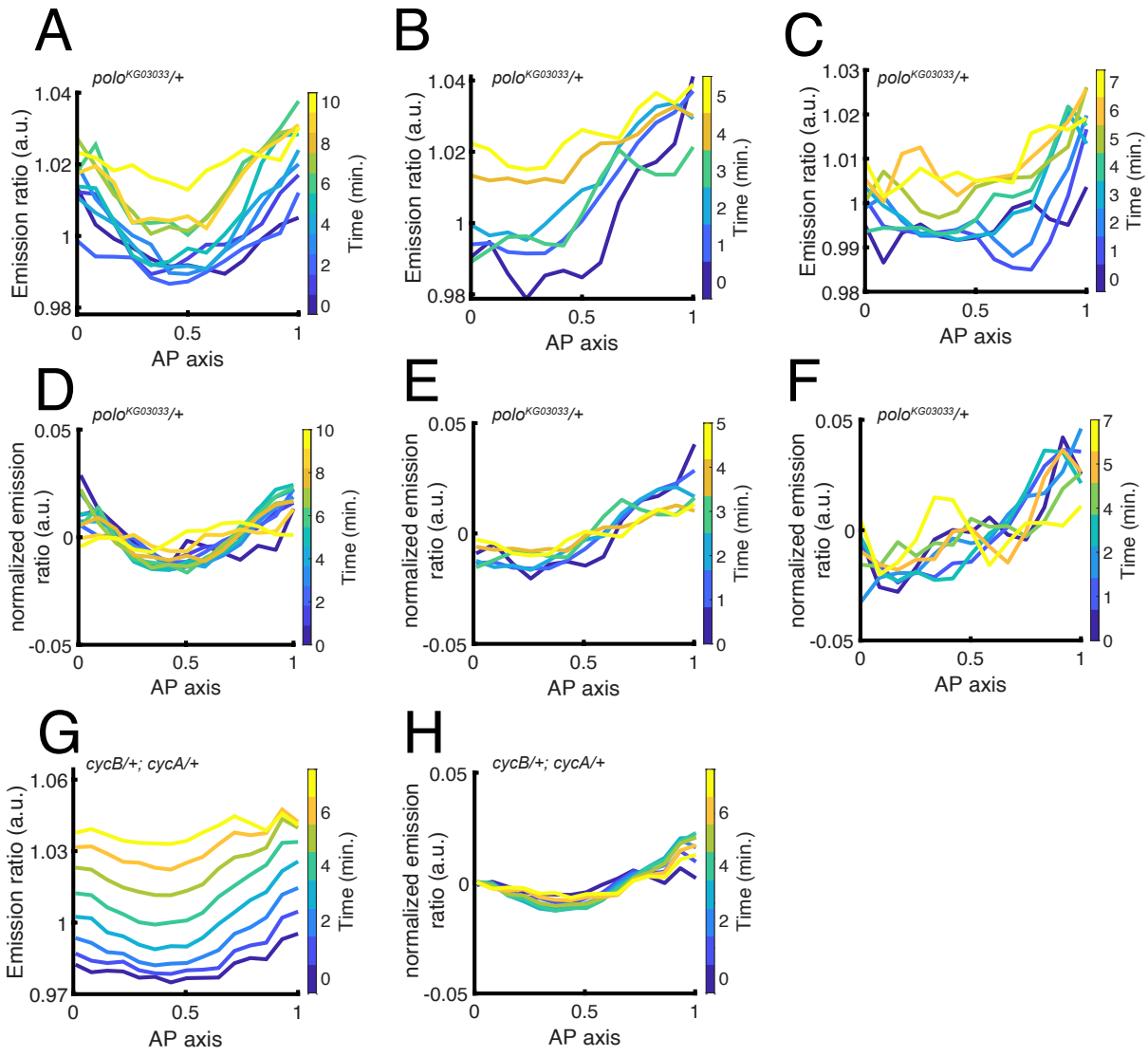

Figure S3. Wave rescaling of *polo* and *cyclin* mutants. Spatial profiles of normal (A-C, G) and rescaled (D-F, H) Cdk1 activities of *polo* (A-F) and *cyclin* (G, H) mutants.

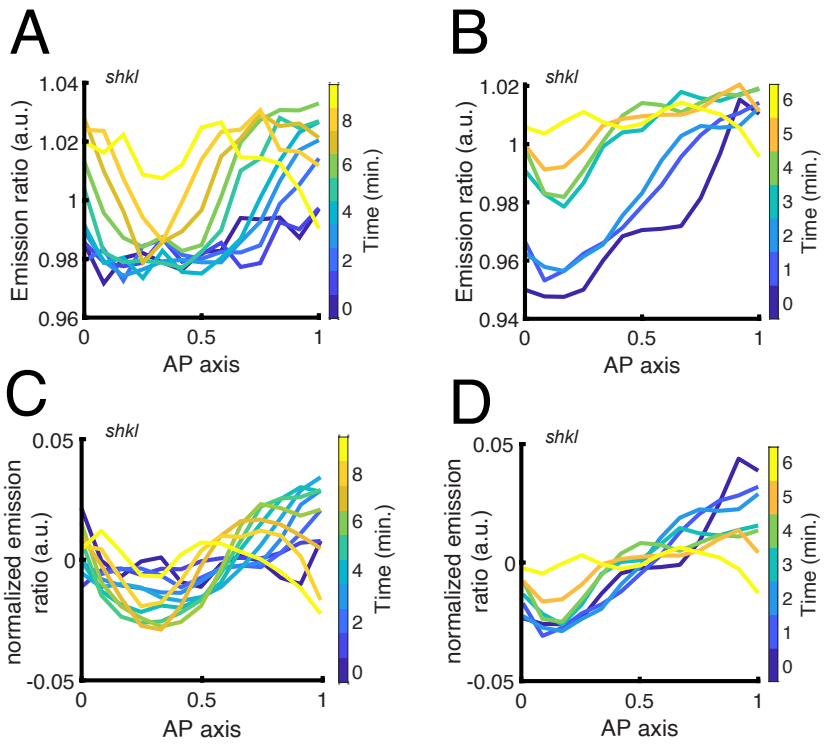

Figure S4. Wave rescaling of *cul-5* mutants. Spatial profiles of normal (A, B) and rescaled (C, D) Cdk1 activities of *cul-5* mutants.

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