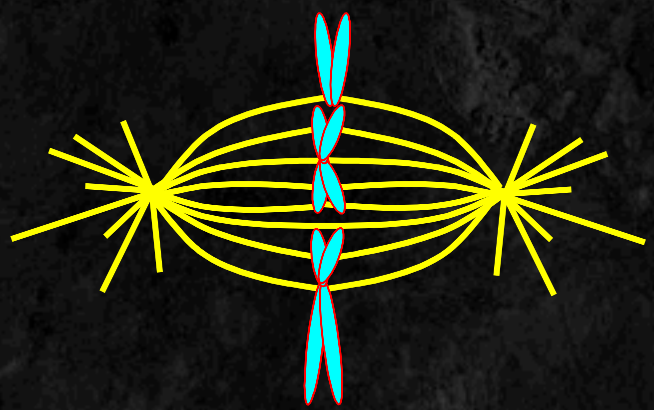
The O'Farrell Lab

Developmental
control
of the cell
cycle

The O'Farrell Lab



Developmental
control
of the cell
cycle

Time

Time

Biological time → Emphasis on clocks & oscillators

Circadian clock
Segmentation oscillator
Cell cycle “oscillator”

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Biological time → Emphasis on clocks & oscillators

- Circadian clock
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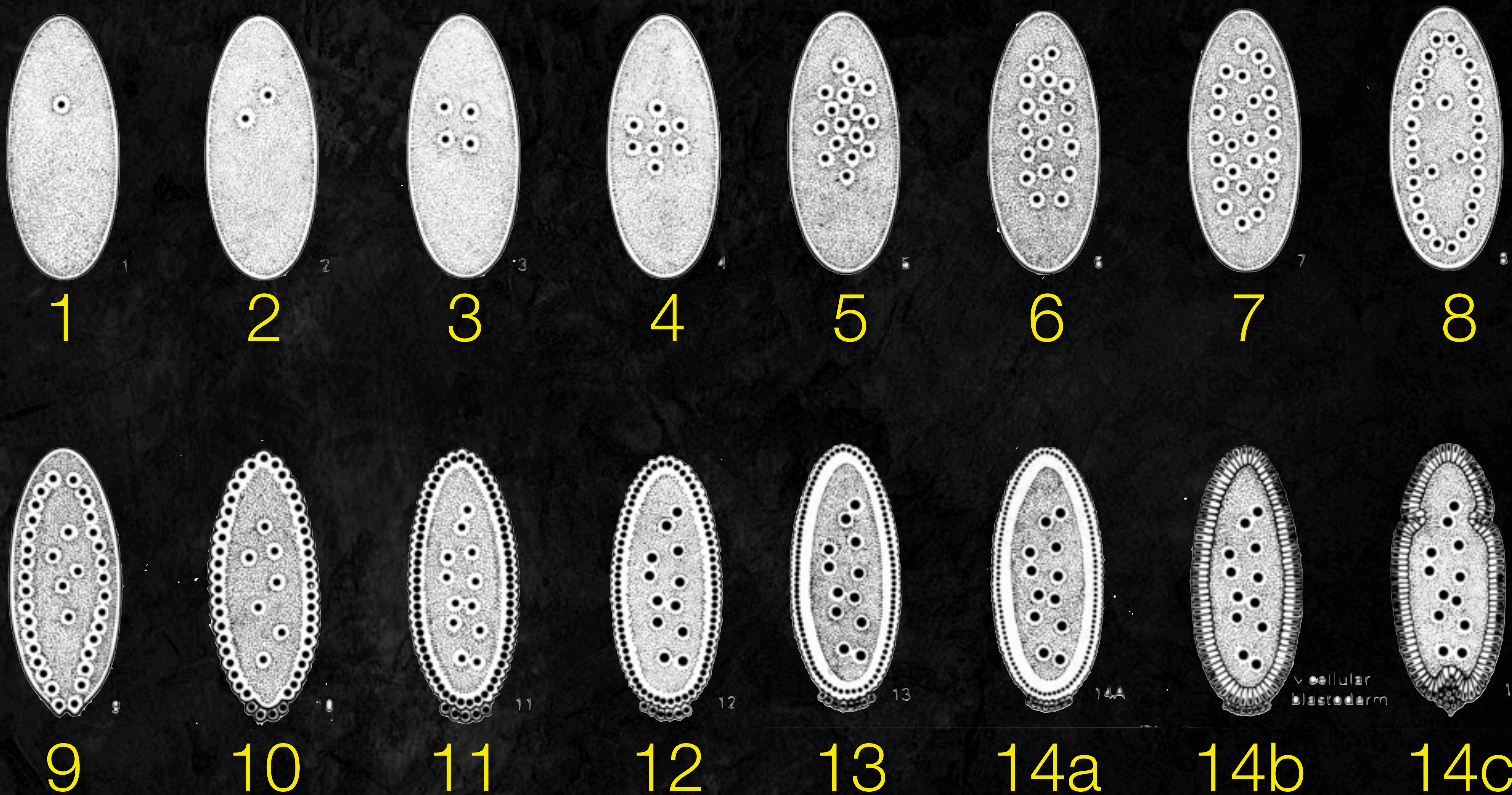
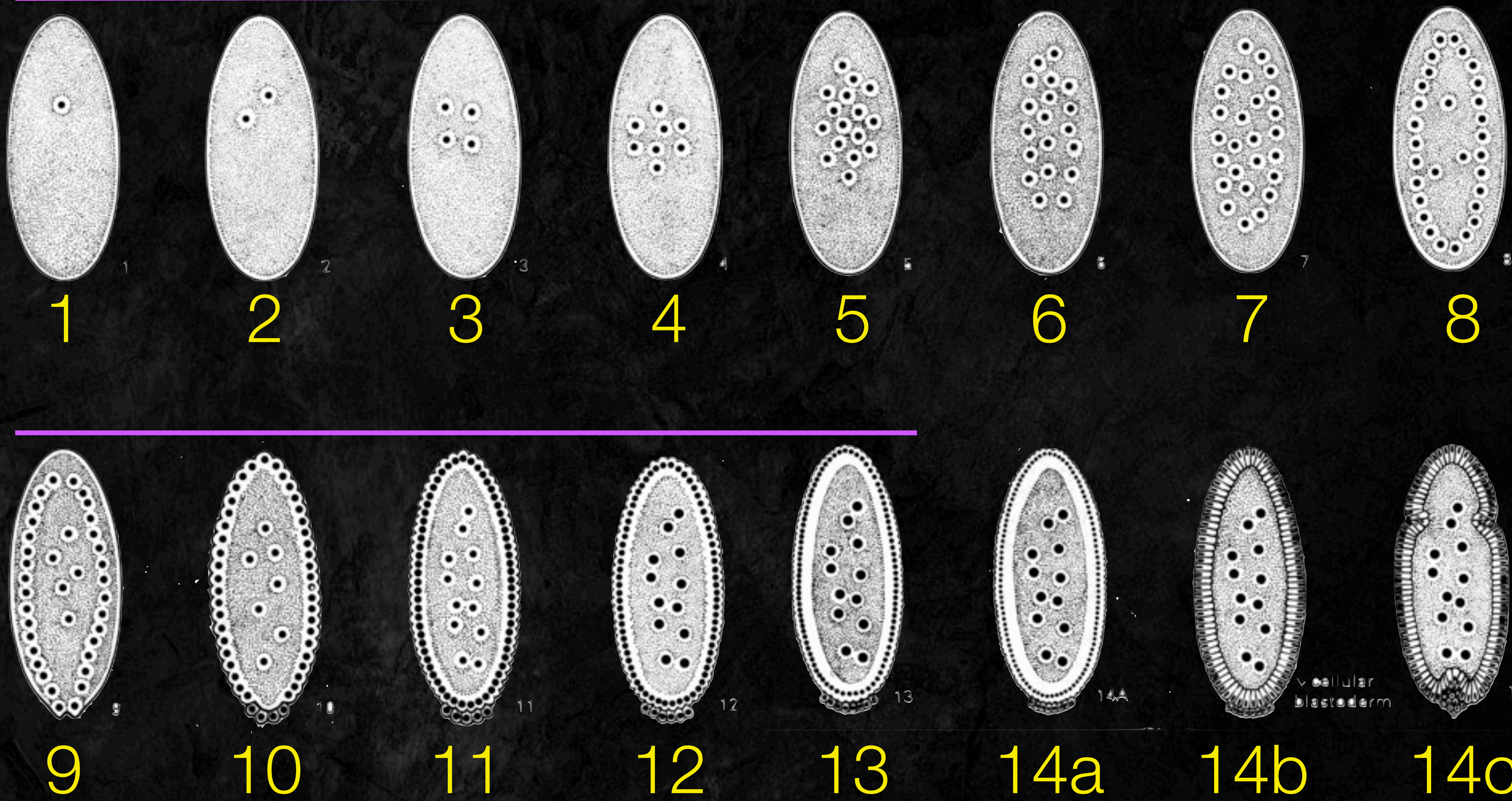
But time is another dimension in development and in life

The Early Fly Cycles



The Early Fly Cycles

syncytial cycles



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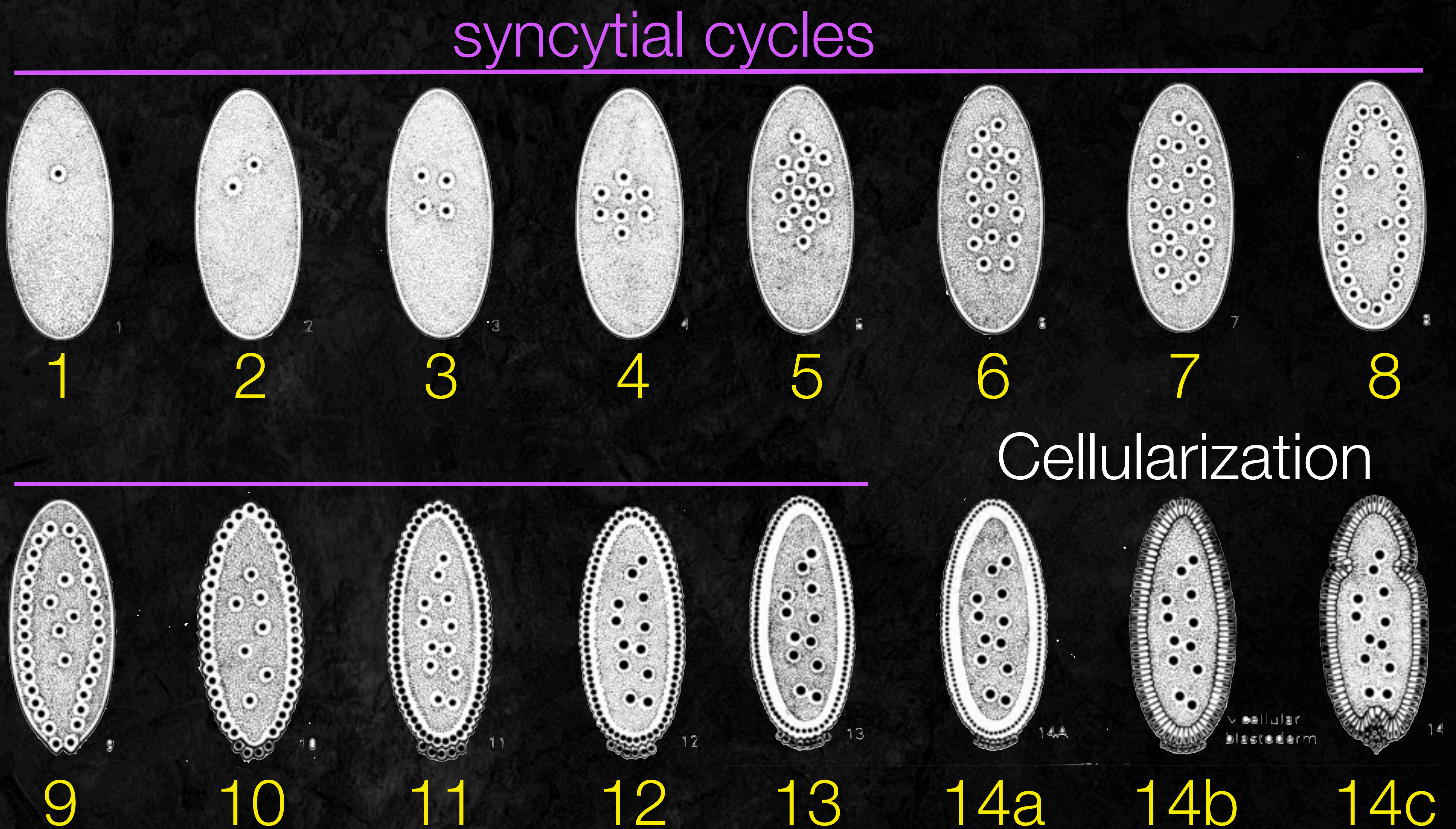

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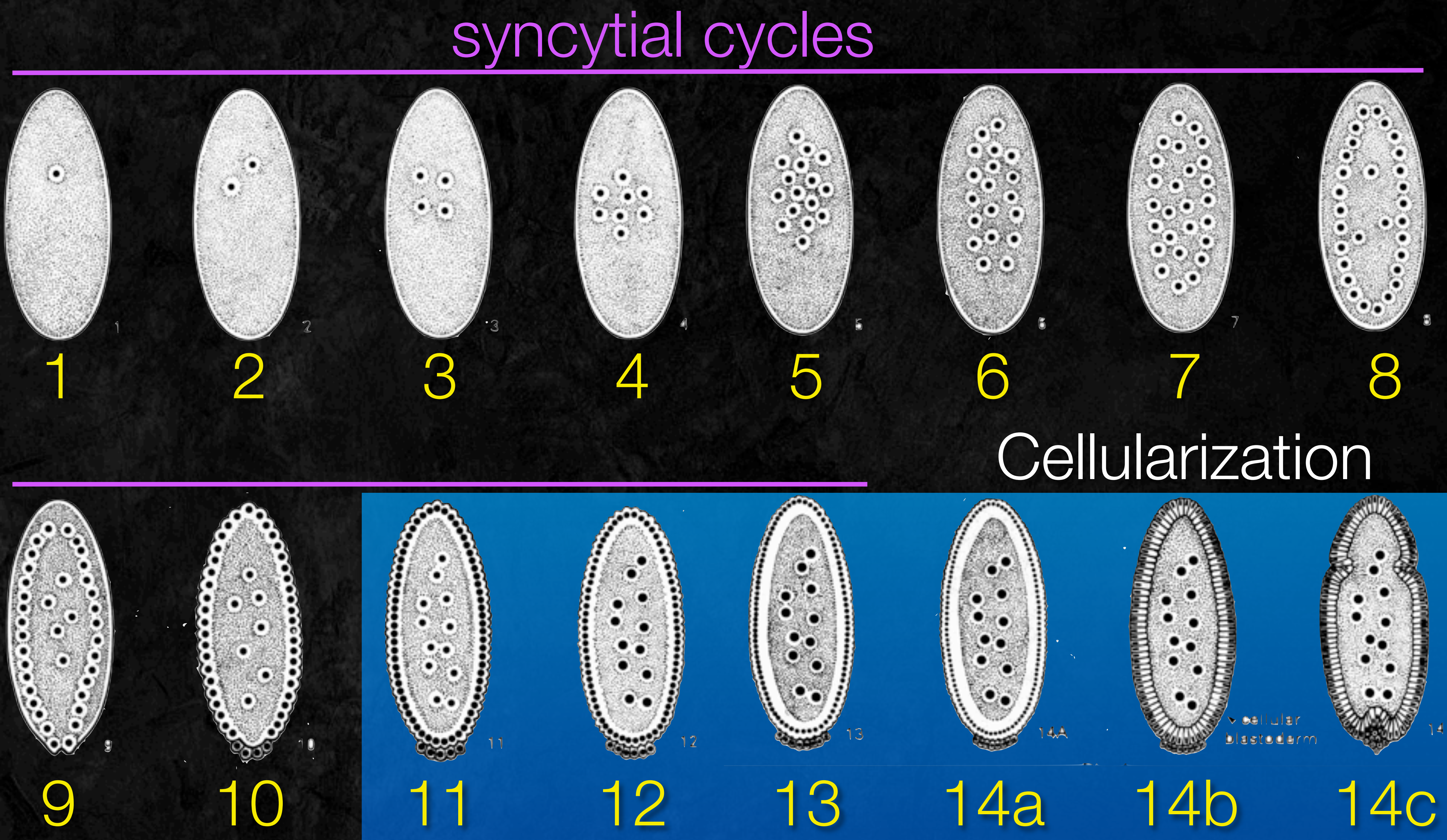

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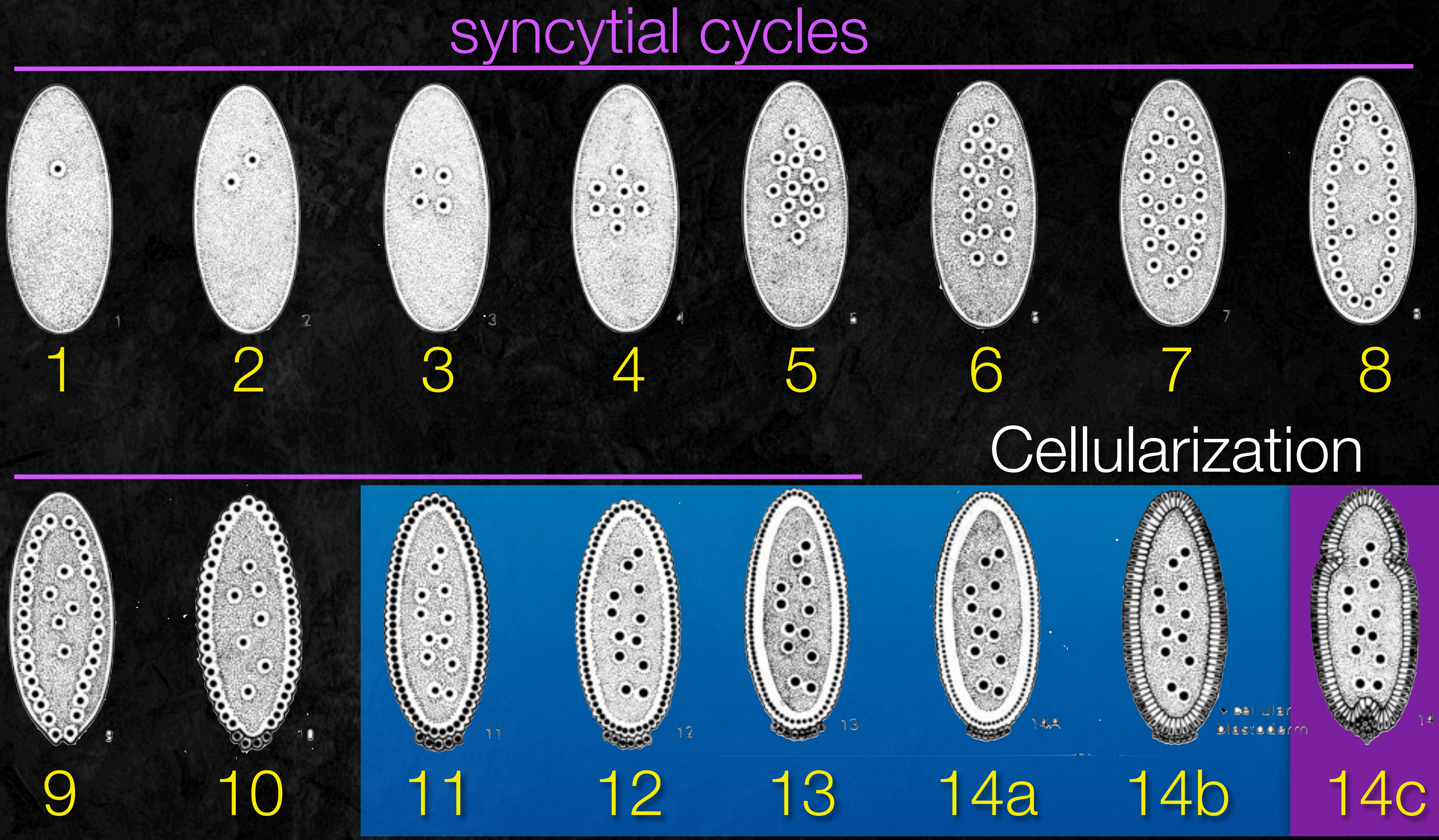

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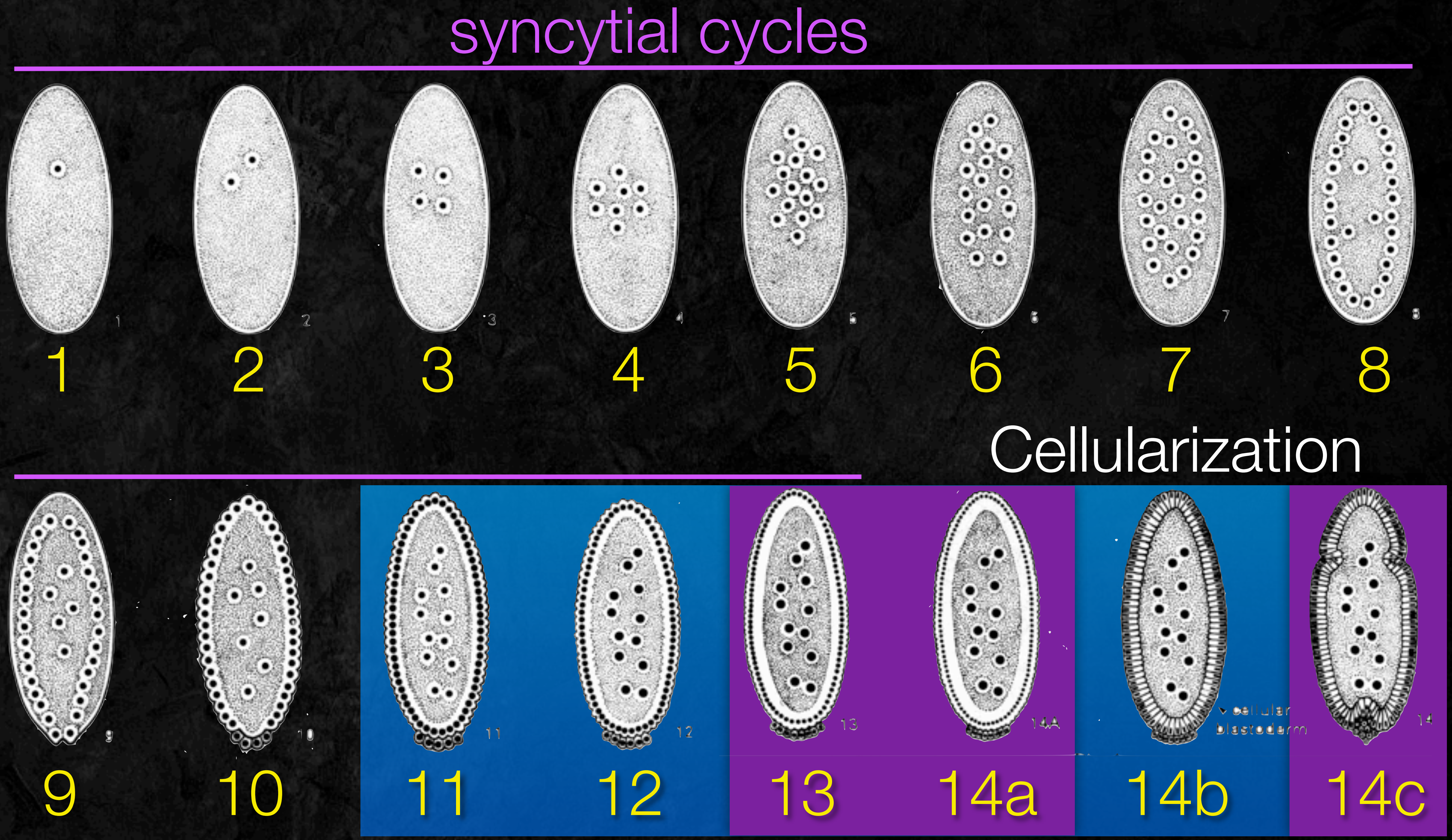

The early Drosophila embryo

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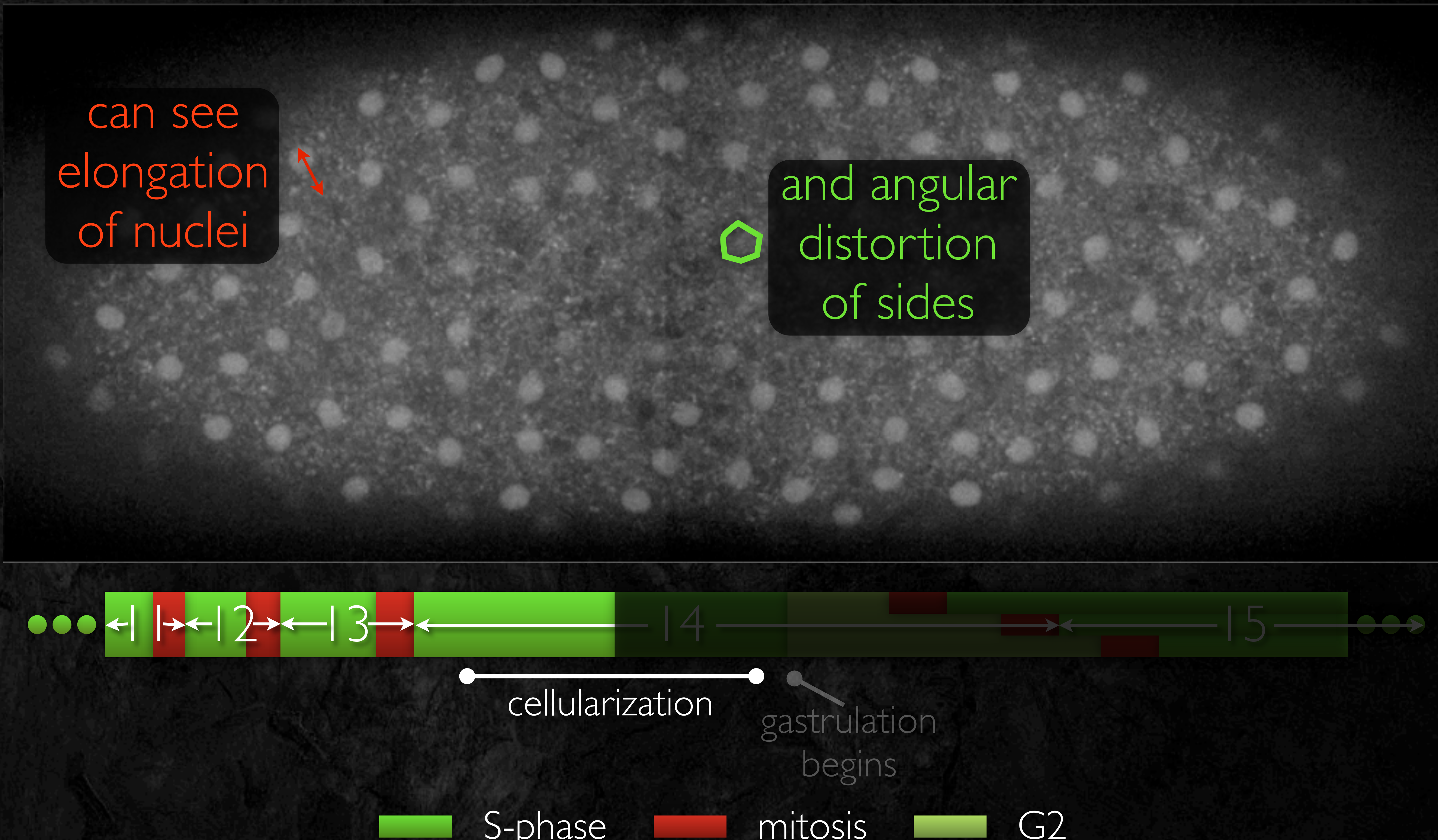
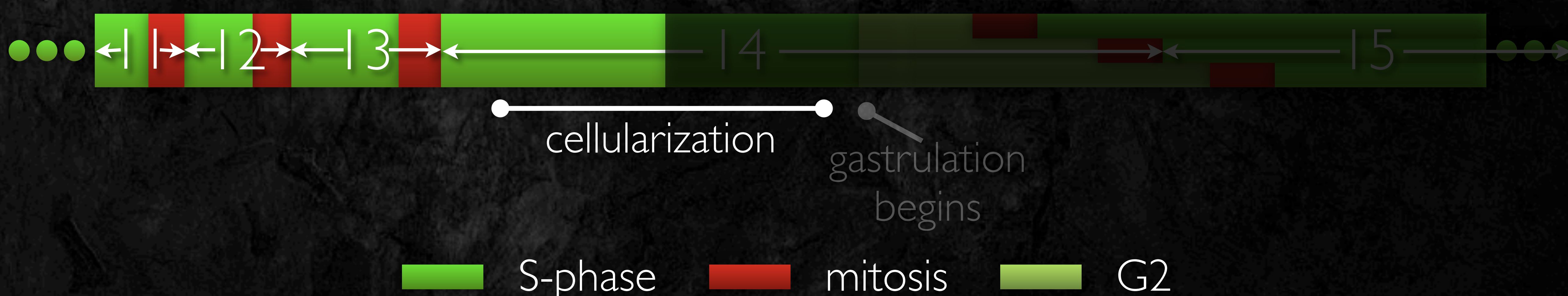


The early Drosophila embryo

can see elongation of nuclei

and angular distortion of sides



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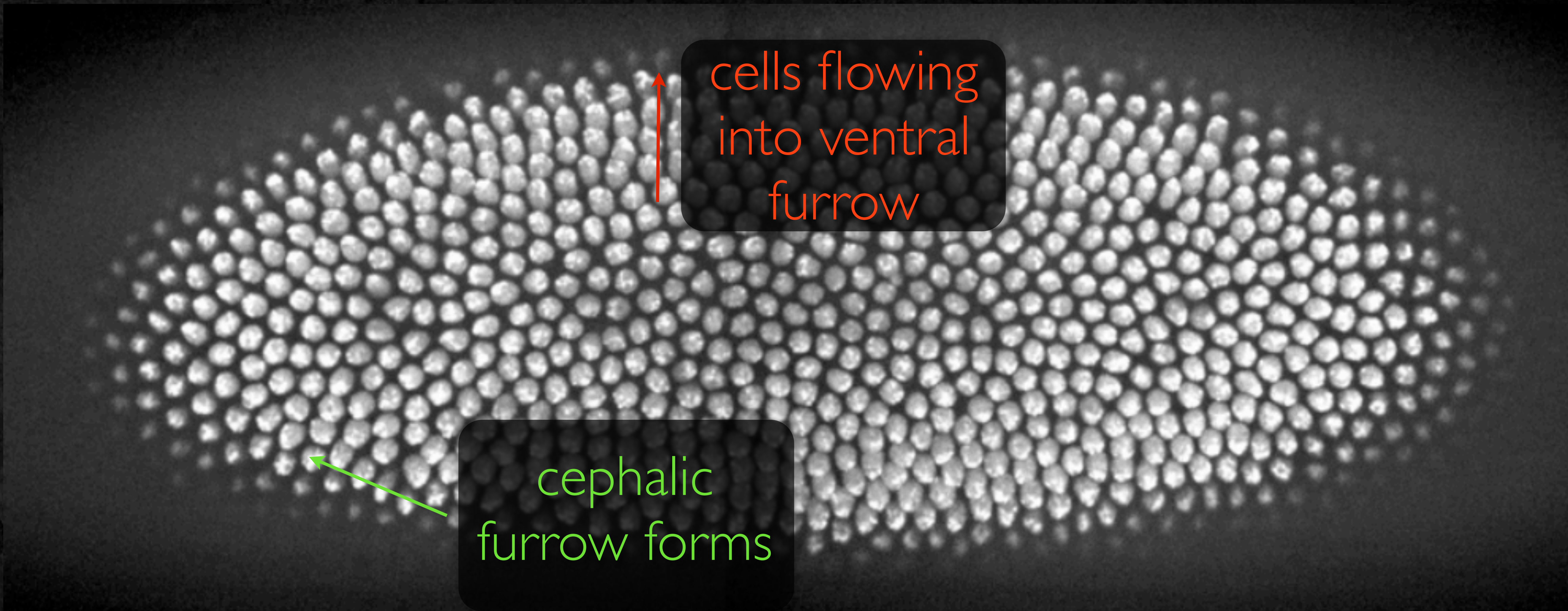
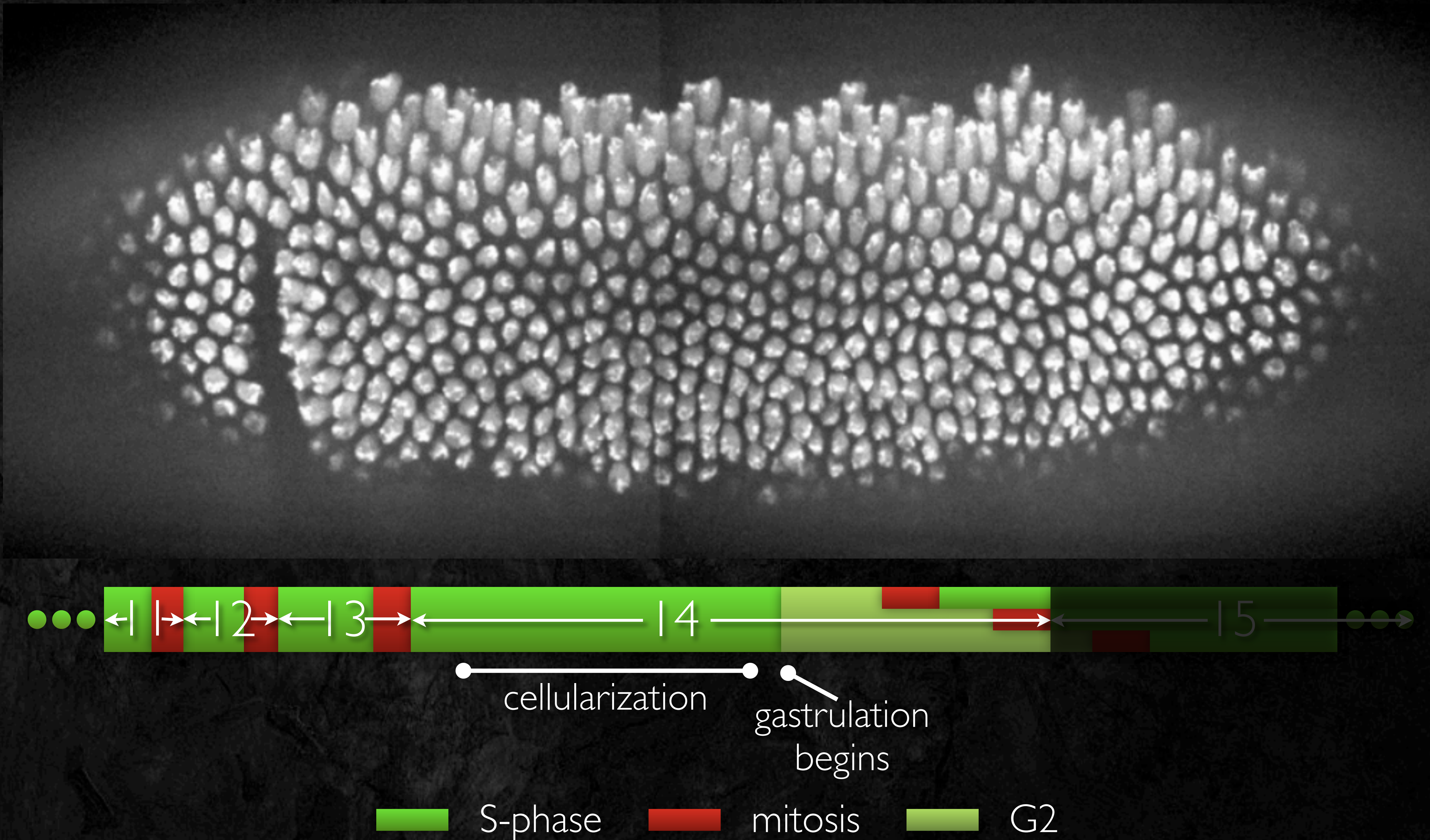


The early Drosophila embryo

cells flowing into ventral furrow

cephalic furrow forms

The early Drosophila embryo



Deep Thinking About Time

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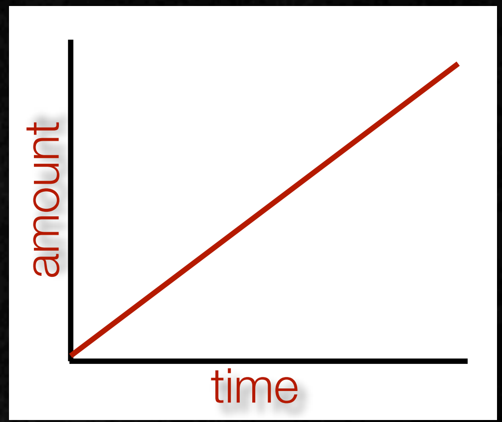

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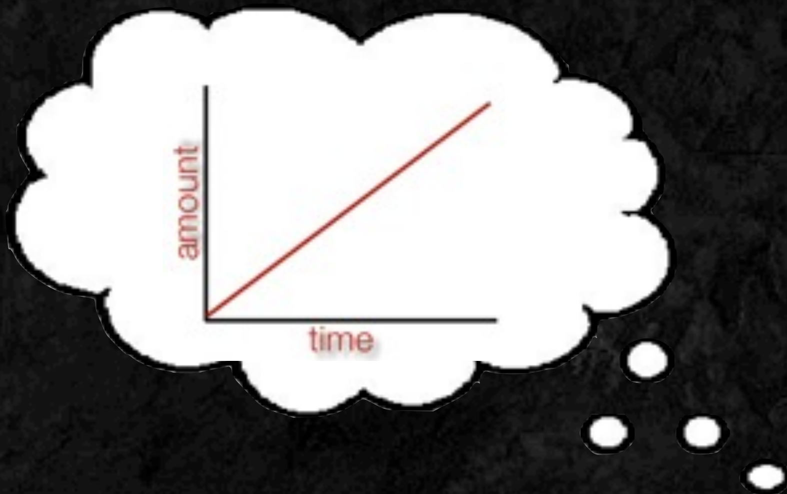

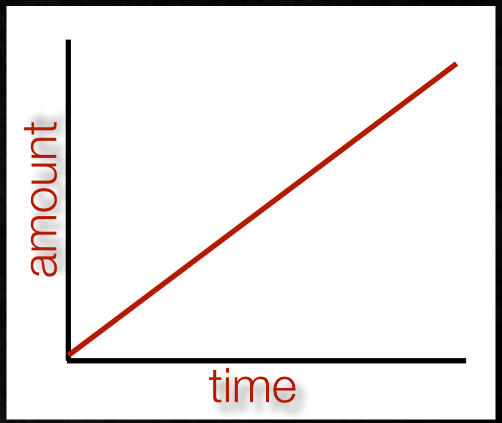

What regulates the spatio-temporal pattern of mitosis?

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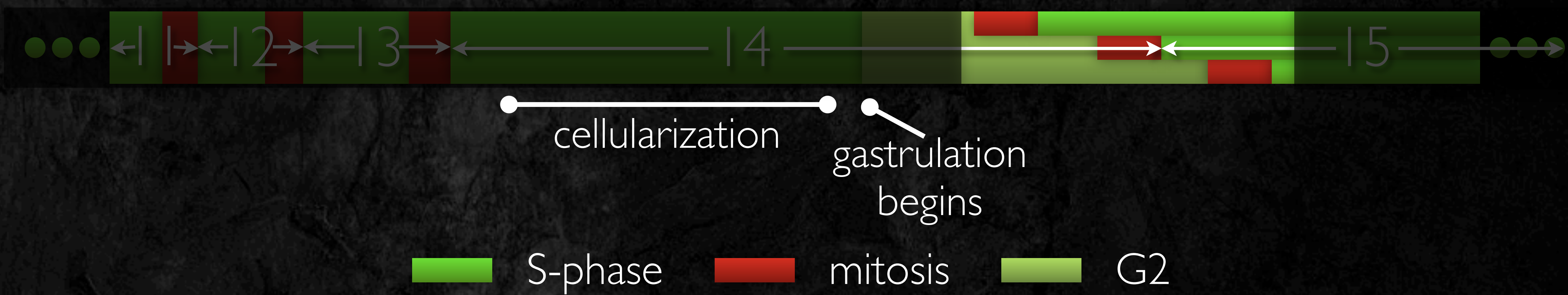

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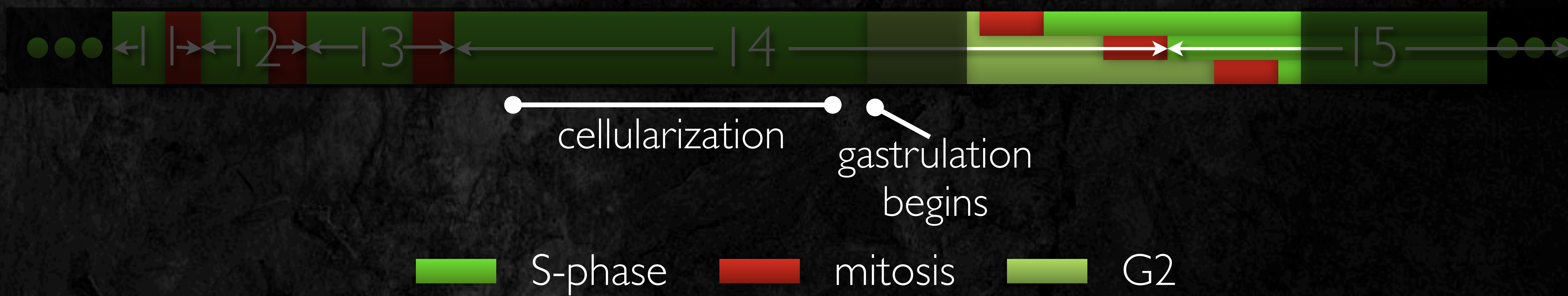
Mitosis 13



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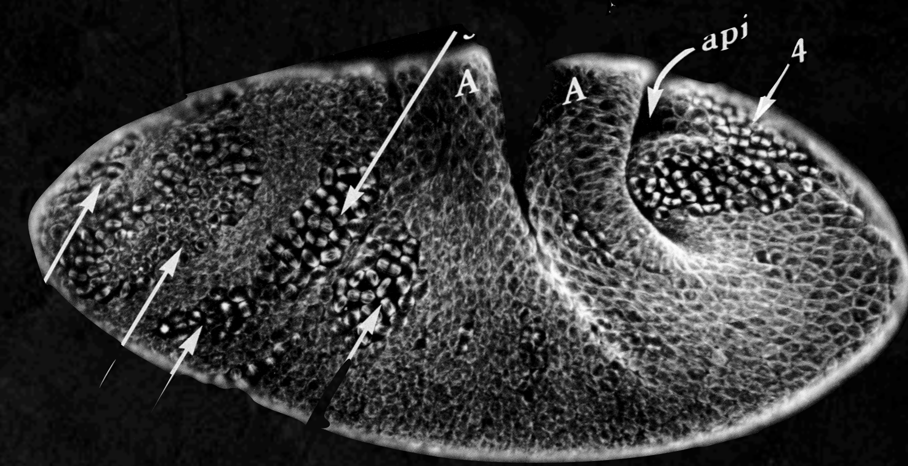
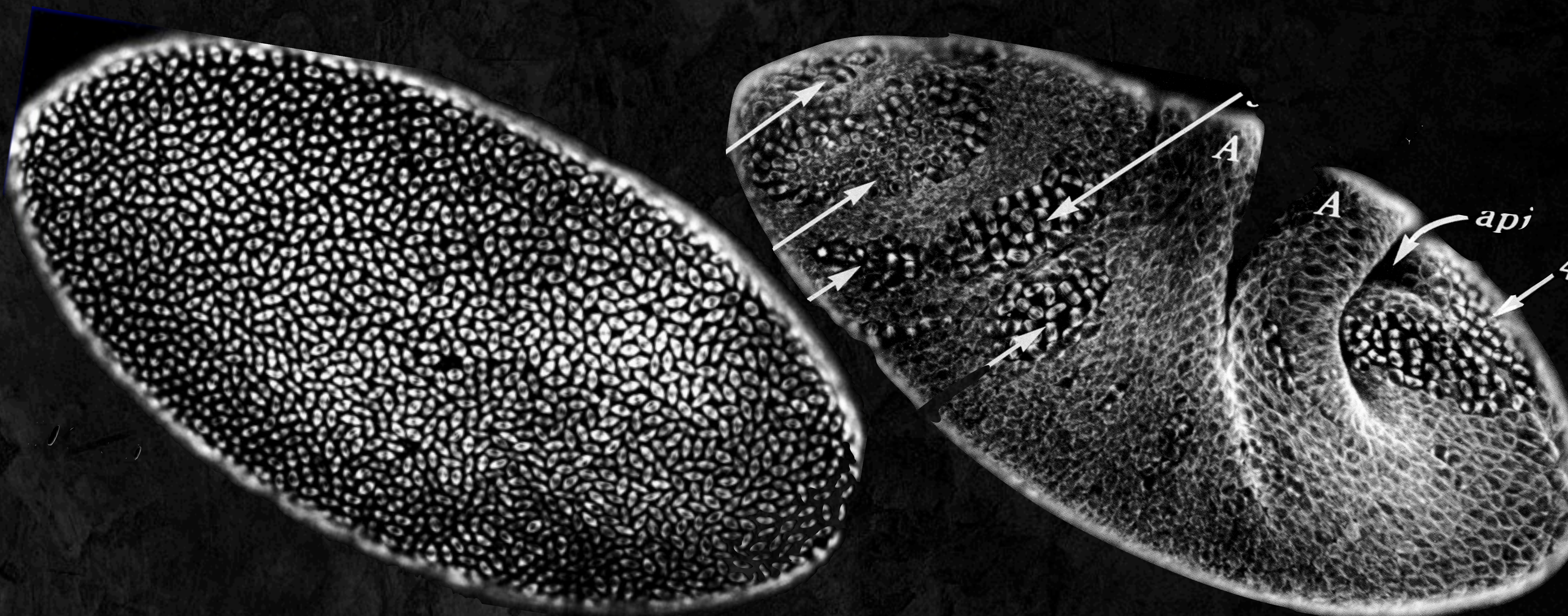


Mitosis 14

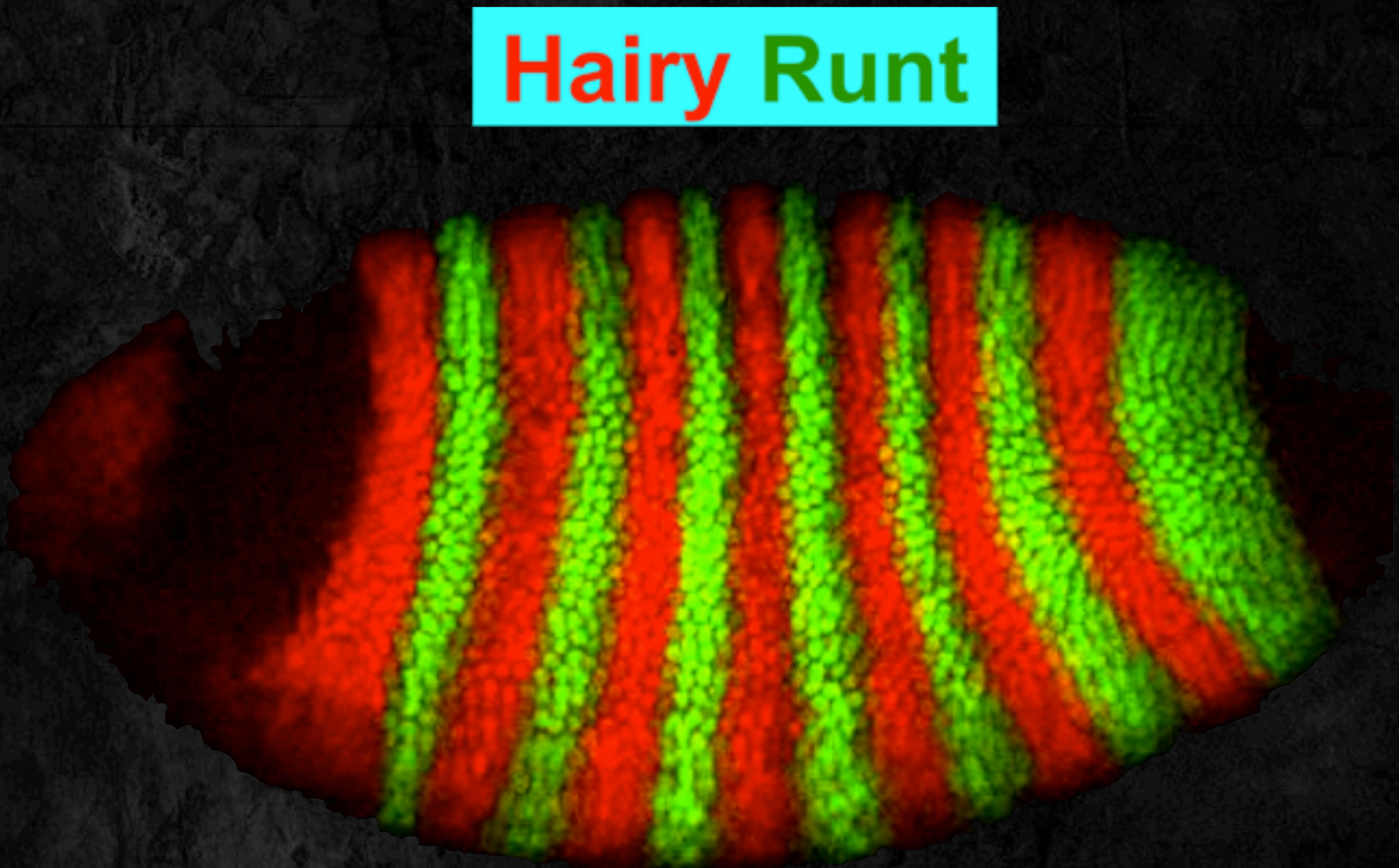
Each of 6000 cells seems to know what to do and when. How?



Mitosis 13 Mitosis 14

Cells in different positions spend different amounts of time in cycle 14 - patterned division

Positional information



In cycle 14, local expression of patterning genes establish a coordinate system - guides events.

Model - patterning genes control where and when a mitotic activator is expressed

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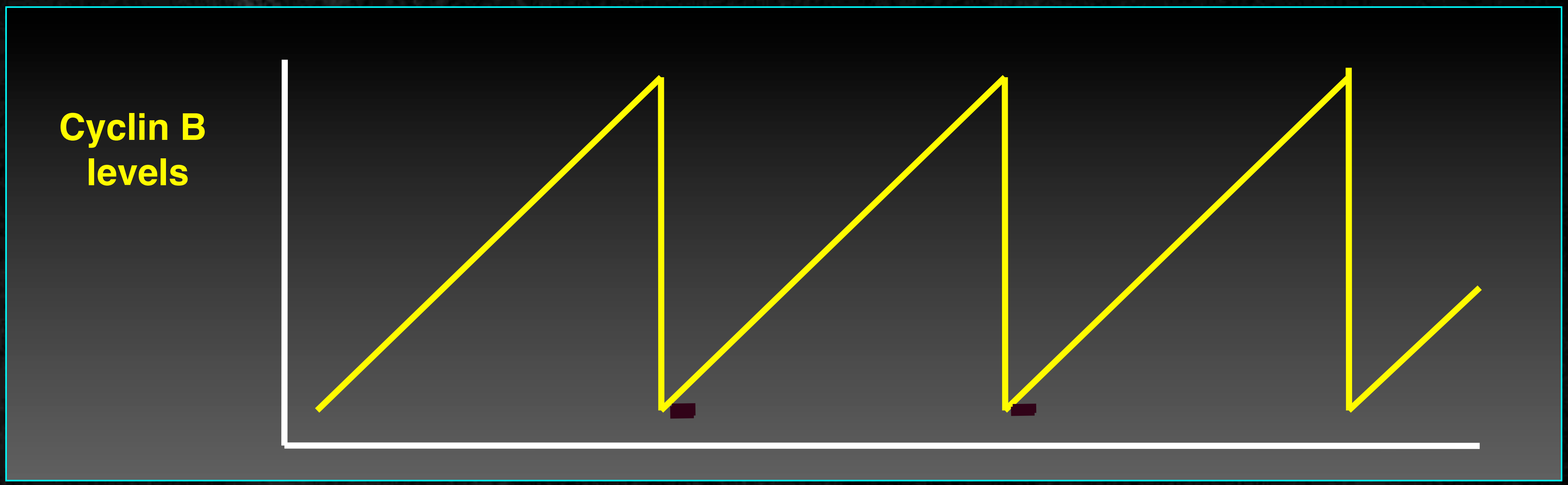
Cyclin was a favored candidate for regulator



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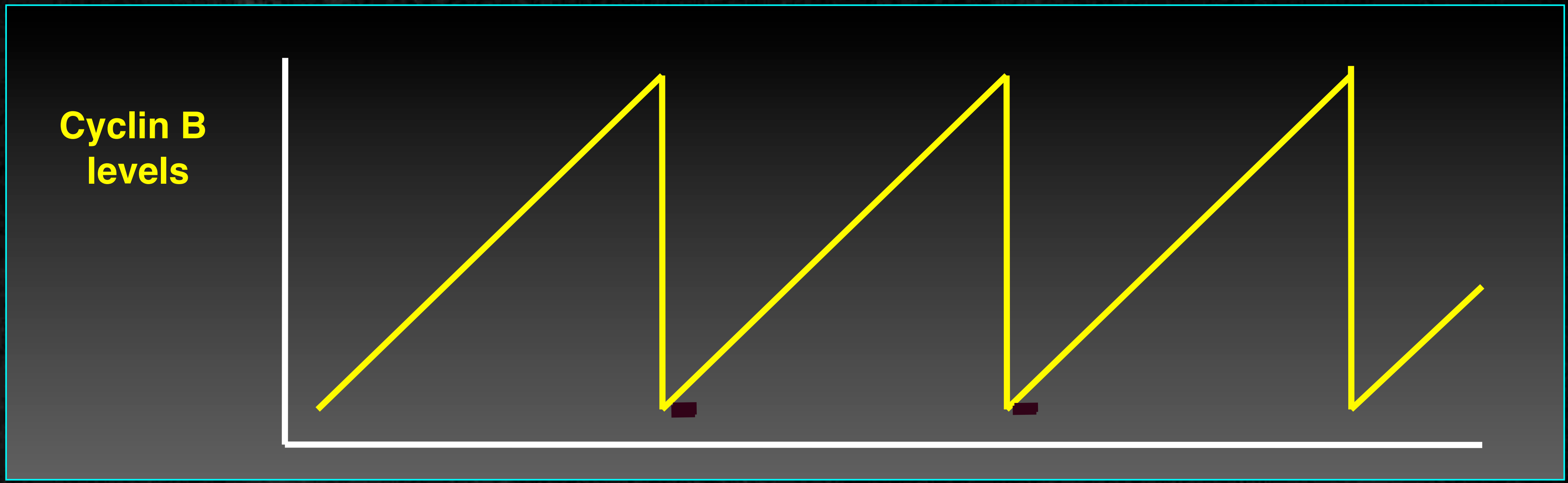

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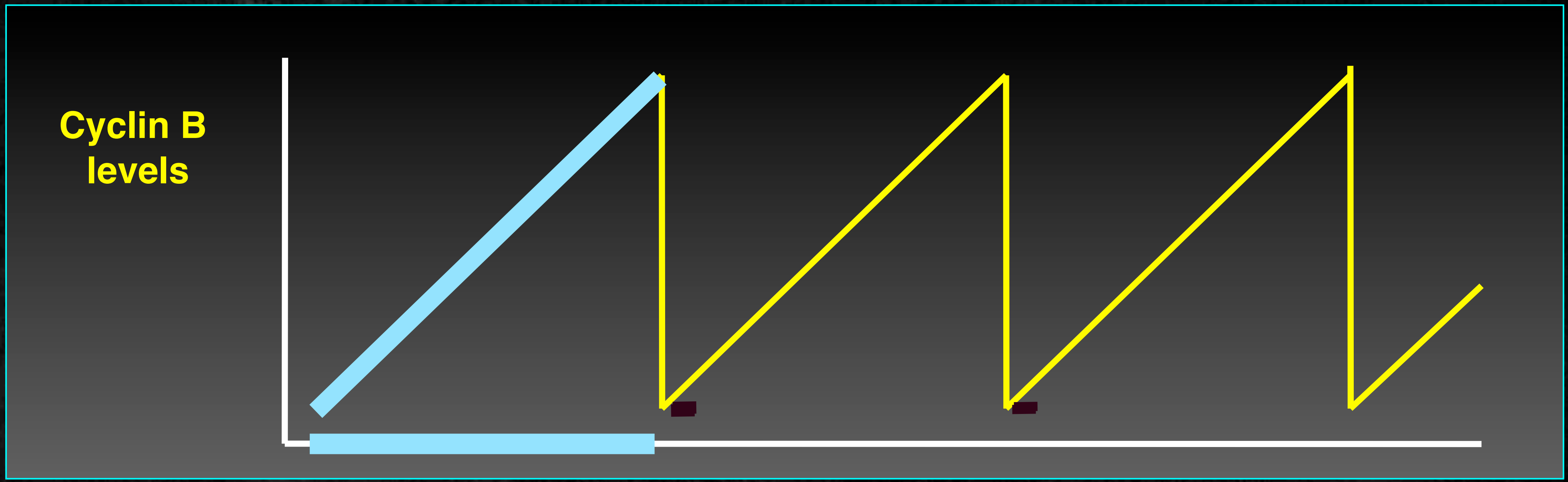

- Cyclin B accumulates to a threshold
- it triggers mitosis

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10

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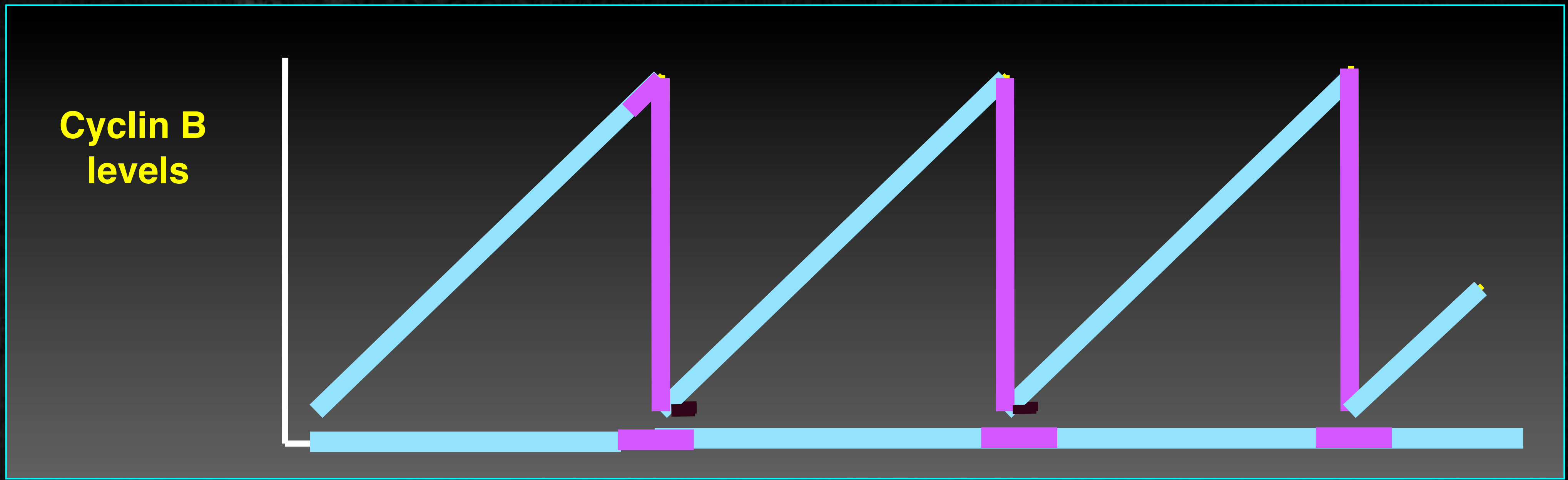
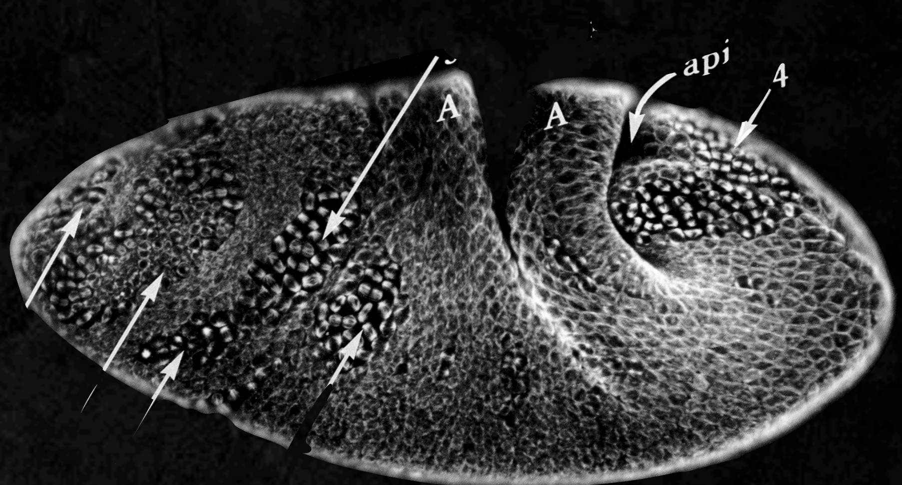


- Cyclin B accumulates to a threshold
- it triggers mitosis
- mitotic degradation resets the clock
- cyclins drive the cell cycle

10

Testing the role of cyclins

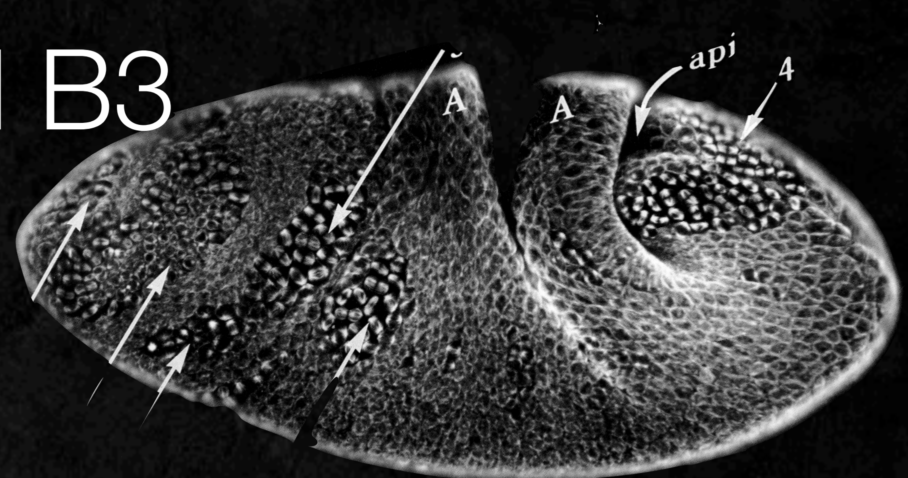


Mitosis 14

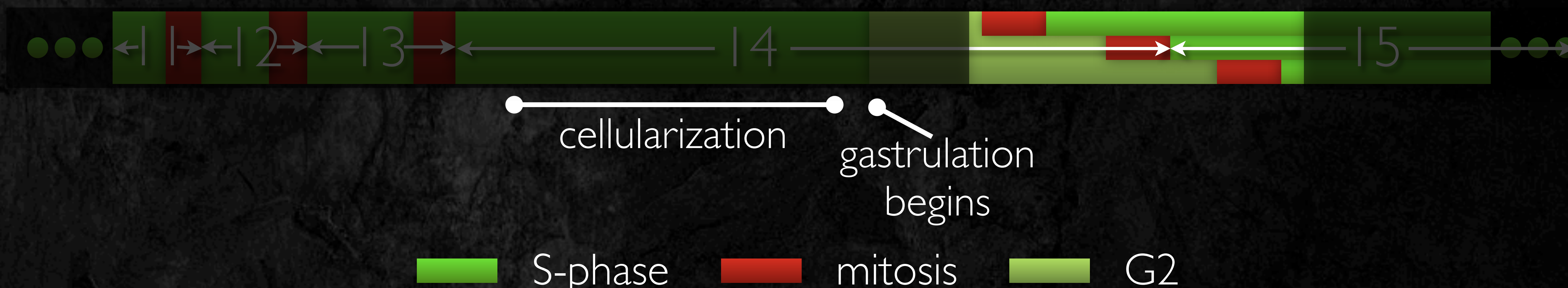
Testing the role of cyclins

Christian Lehner

cloned cyclins A,B and B3
mutants
antibodies
transgenes



Mitosis 14



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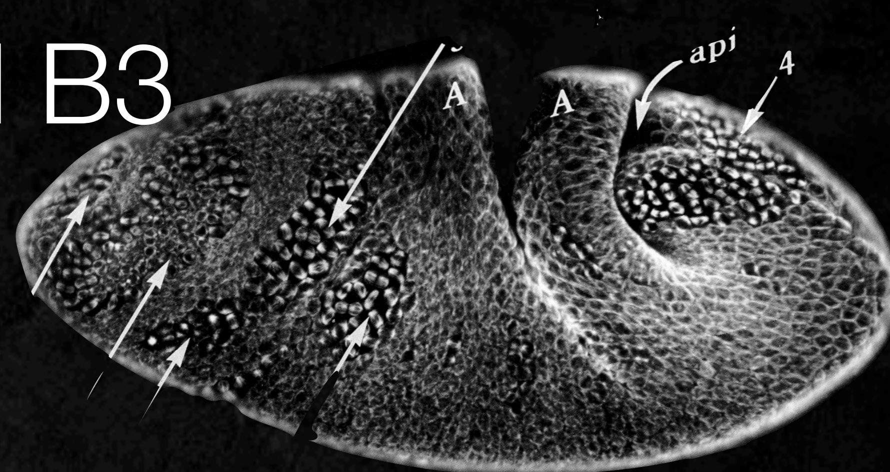
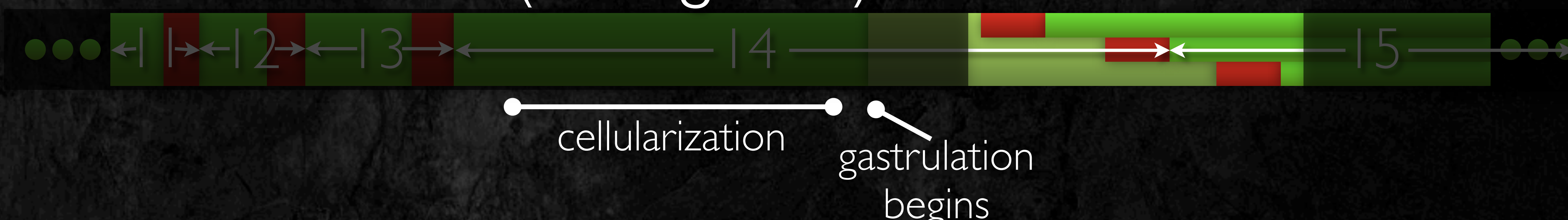


Mitosis 14

expression uniform

reduced level (mutants)

increased level (transgenes)

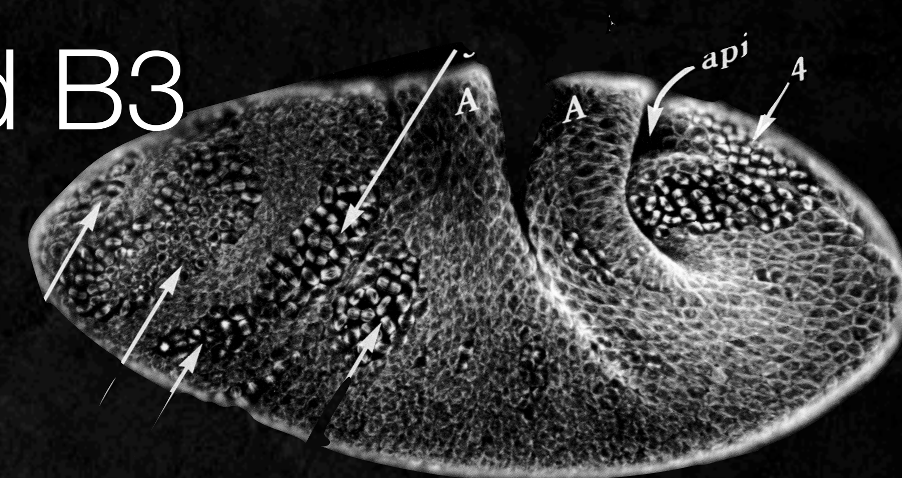


S-phase mitosis G2

Testing the role of cyclins

Christian Lehner

cloned cyclins A,B and B3
mutants
antibodies
transgenes



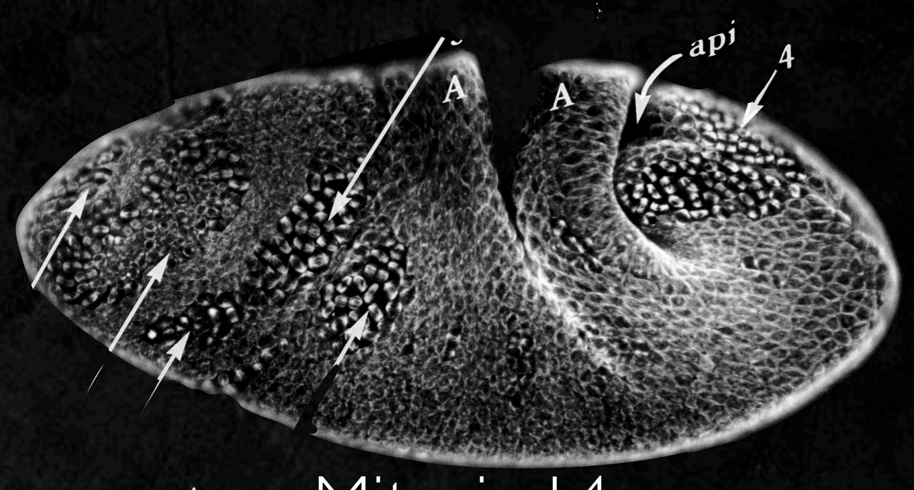
Mitosis 14

expression uniform
reduced level (mutants)
increased level (transgenes)

} timing unaffected

Cyclin levels do not regulate timing of cycle 14

A mutant, *string*, blocked cell cycle progression in G2 of cycle 14



Mitosis 14

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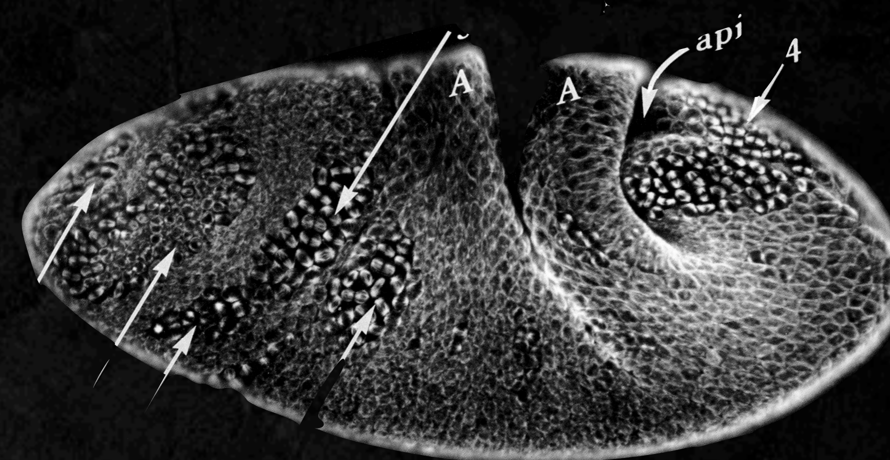
Bruce Edgar



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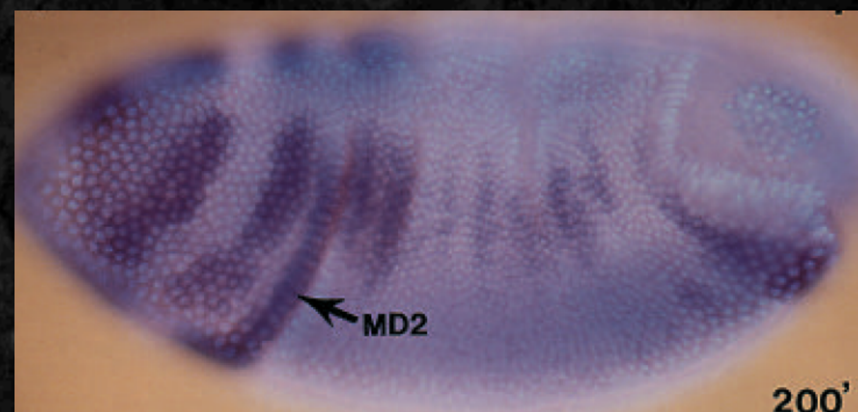
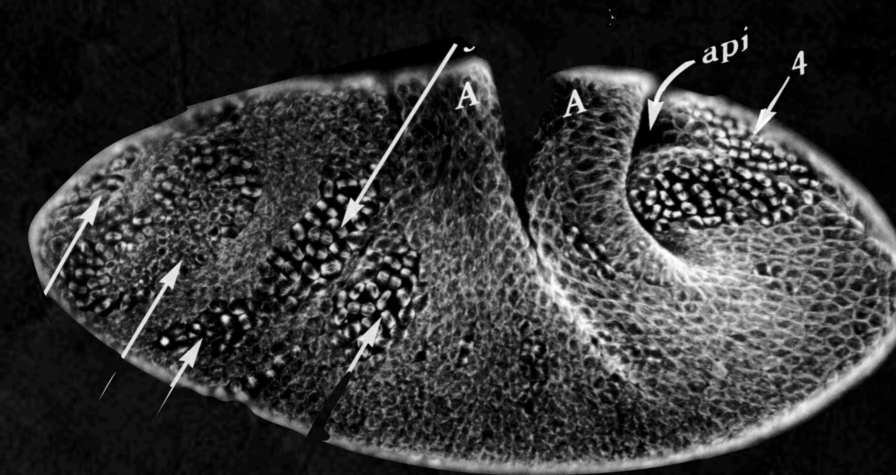


string mRNA @ 200 min



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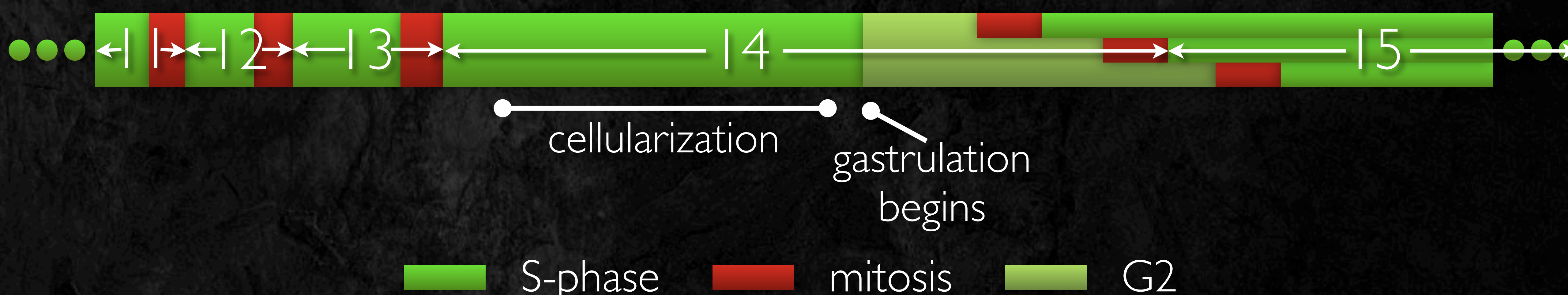

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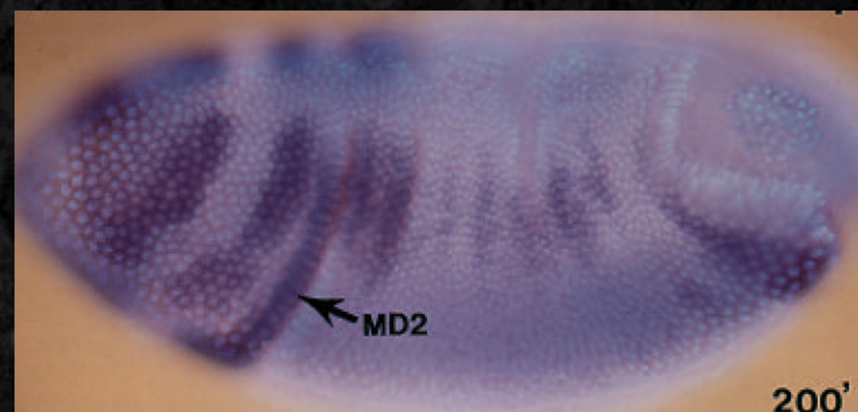

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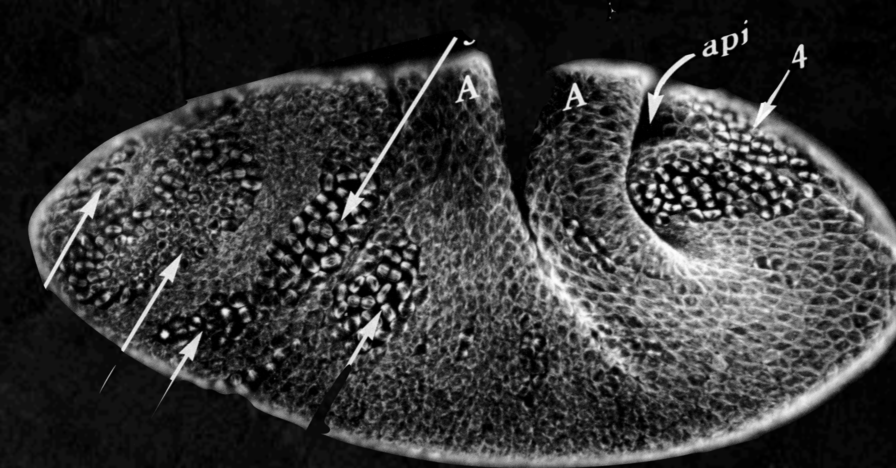

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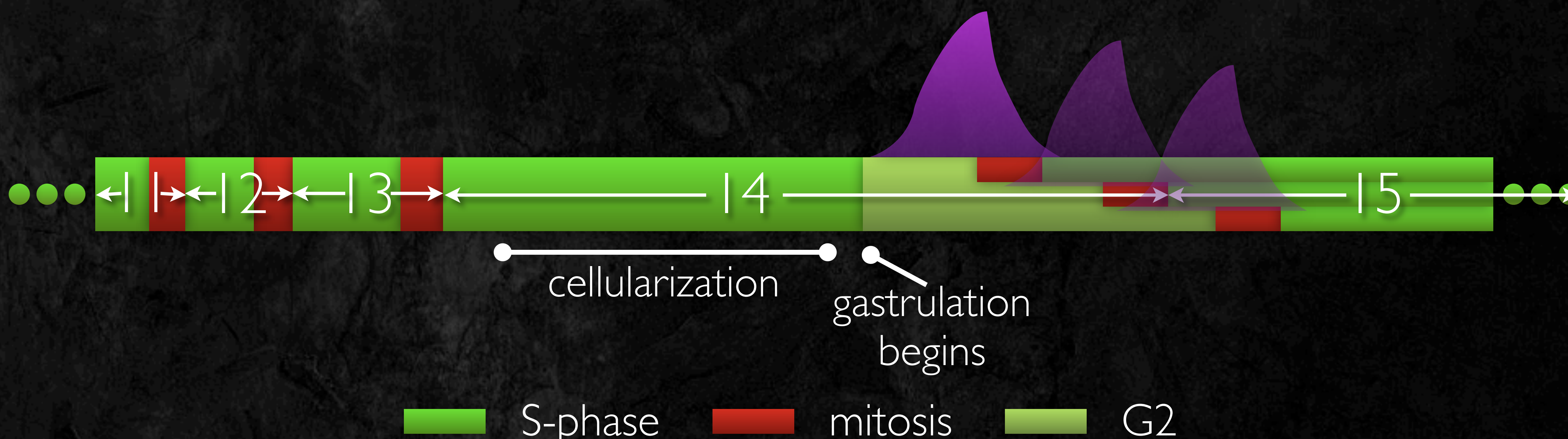

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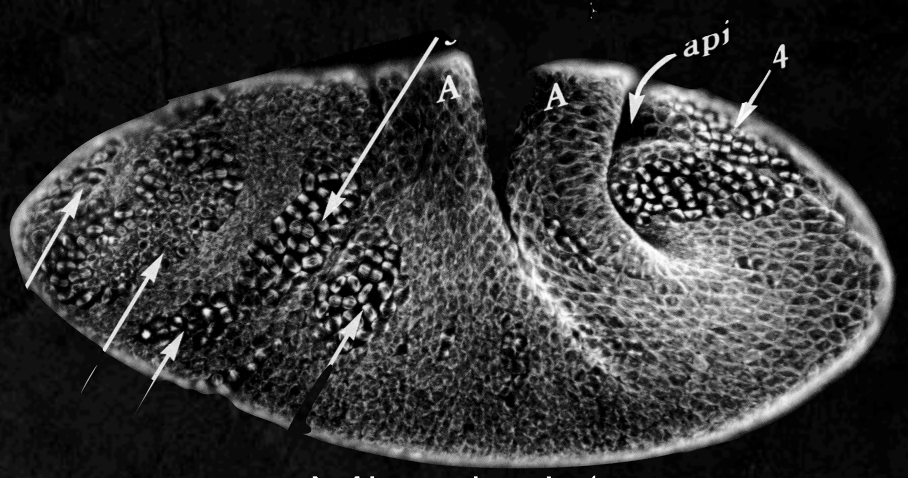

Mitosis 14

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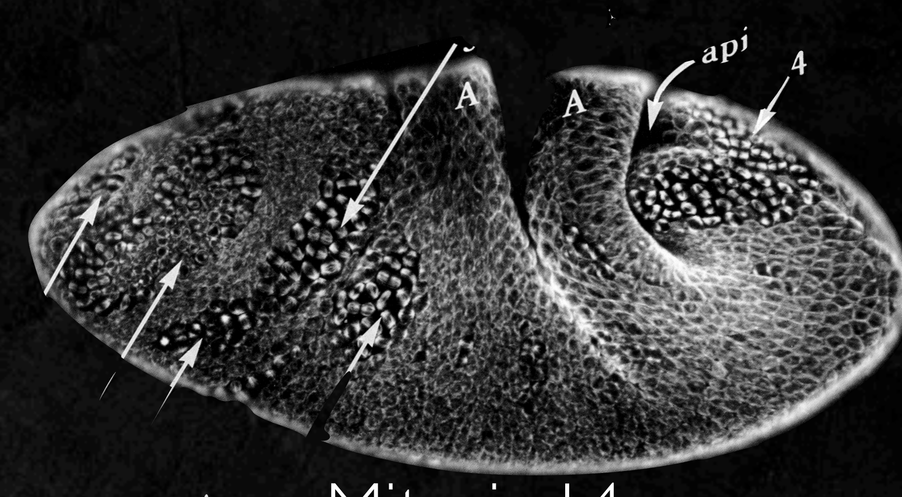
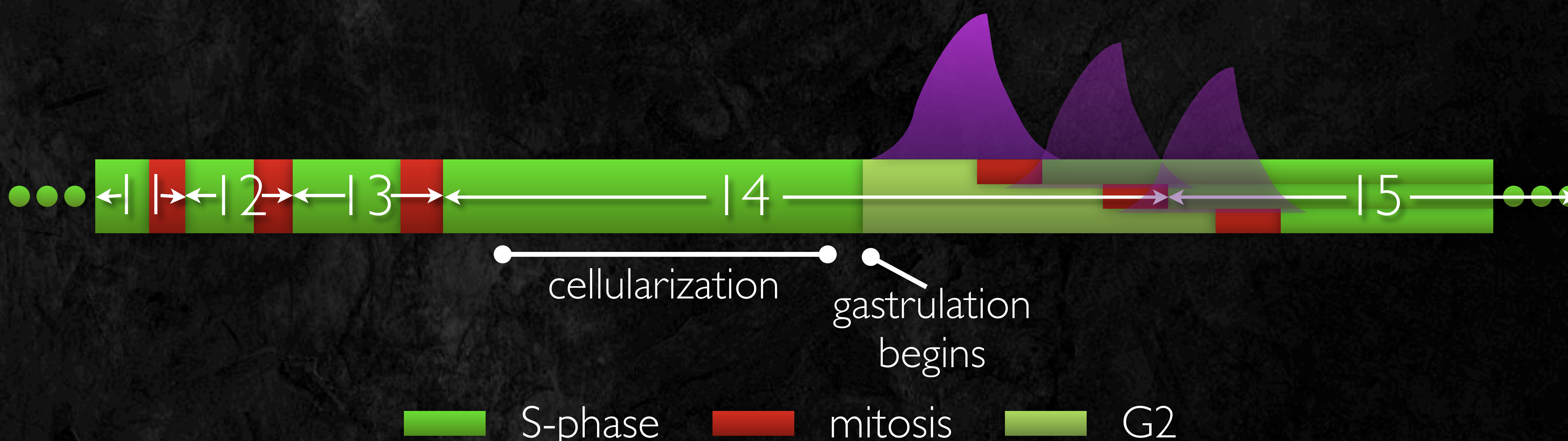
Bruce Edgar

Uniform induced expression gave uniform early mitosis



Mitosis 14



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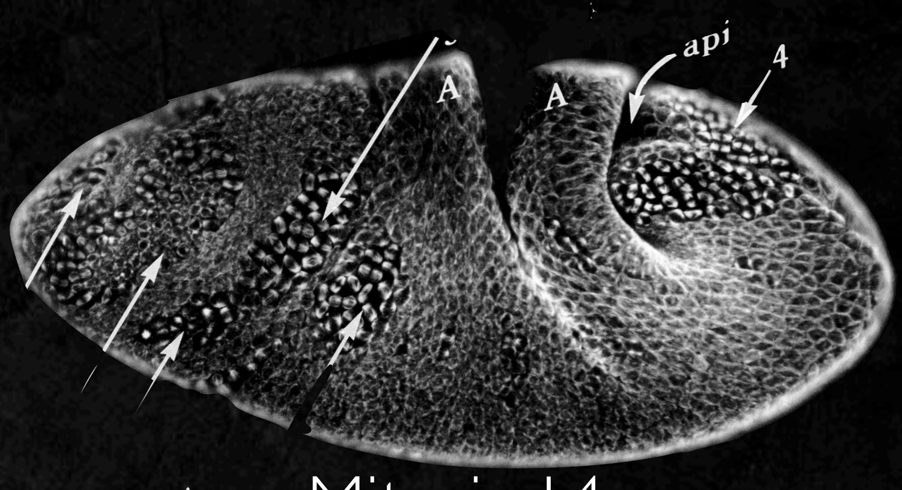
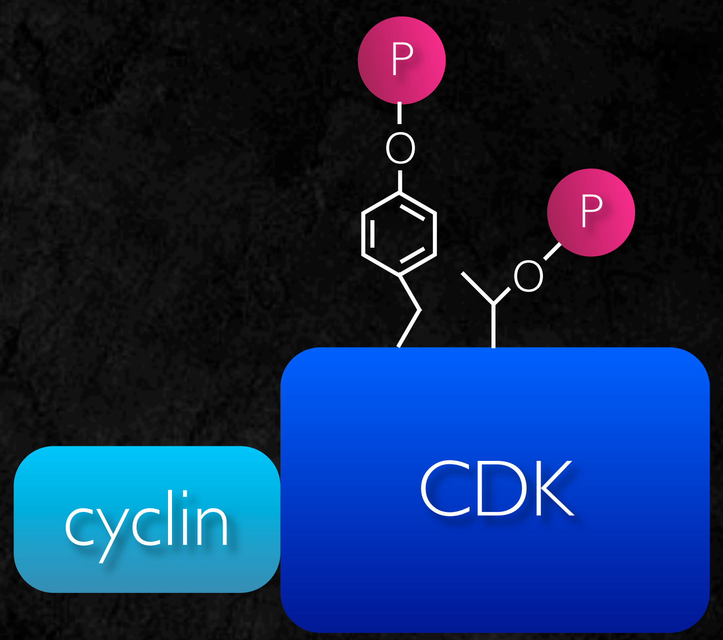


Mitosis 14

Cdc25 activates preformed cyclin:Cdk complexes



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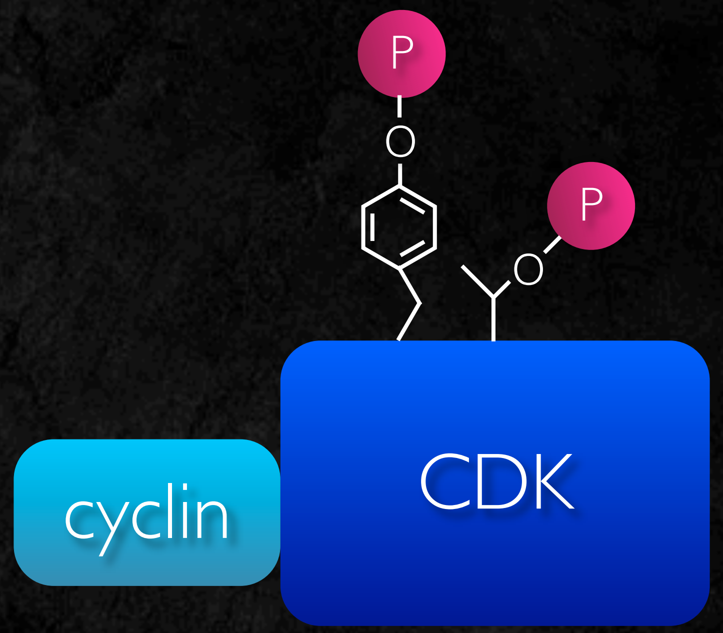
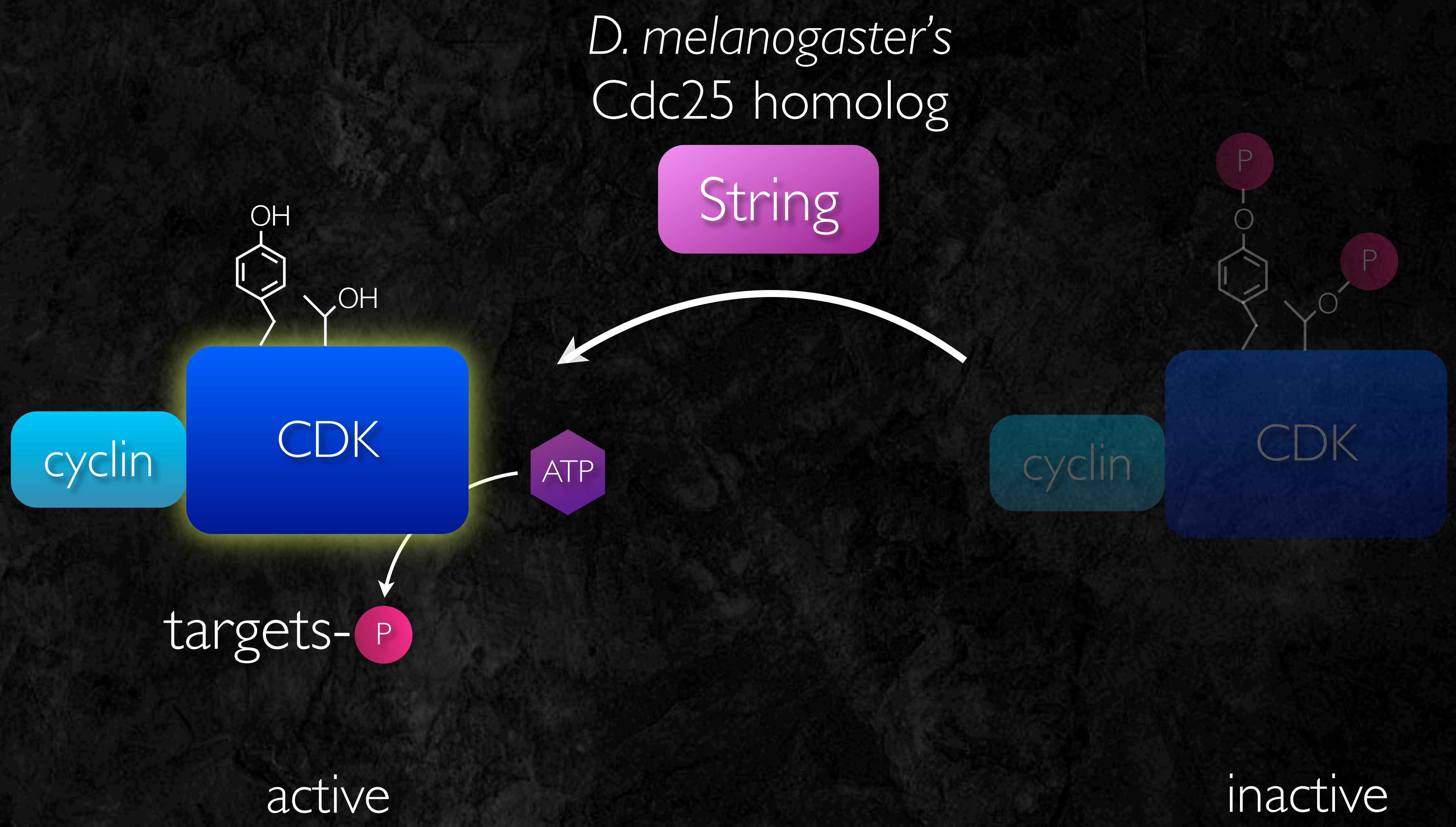


inactive

Cdc25 activates preformed cyclin:Cdk complexes



New transcription of Cdc25^{string} regulates the time of mitosis 14

New transcription of Cdc25*string* regulates the time of mitosis 14

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Directing Morphogenesis

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Directing Morphogenesis

- Control where, when and how much you do things

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Directing Morphogenesis

- Control where, when and how much you do things
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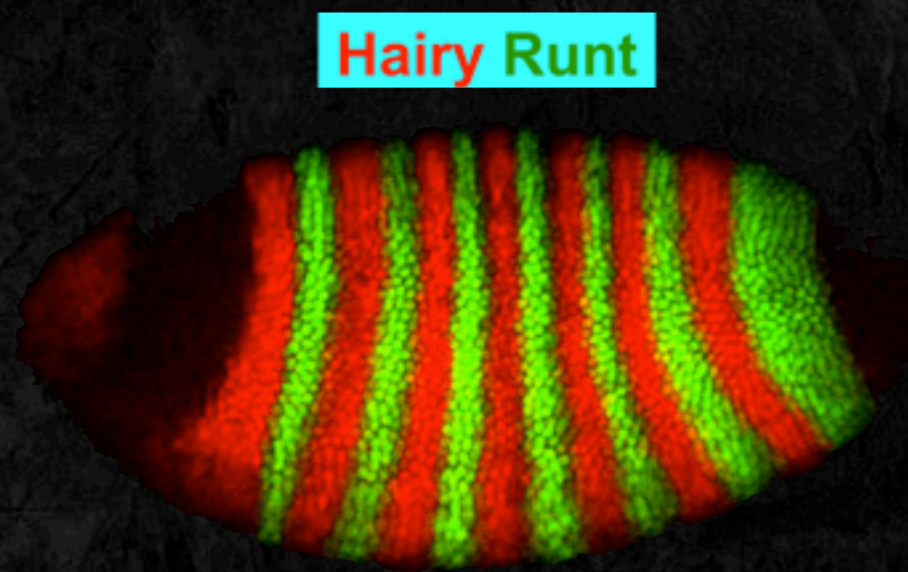
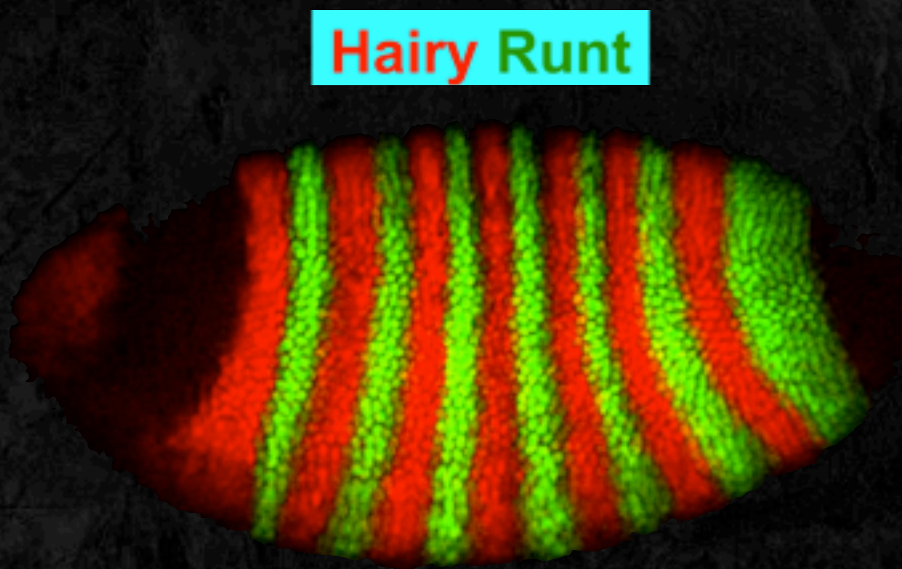
- *string* controls where and when you divide
- other genes control where and when other things happen
- expression of *inscutable* controls orientation of mitosis



Interpreter genes
(e.g. *string*)

Spatially and temporally
regulated cell behaviors

Morphogenesis



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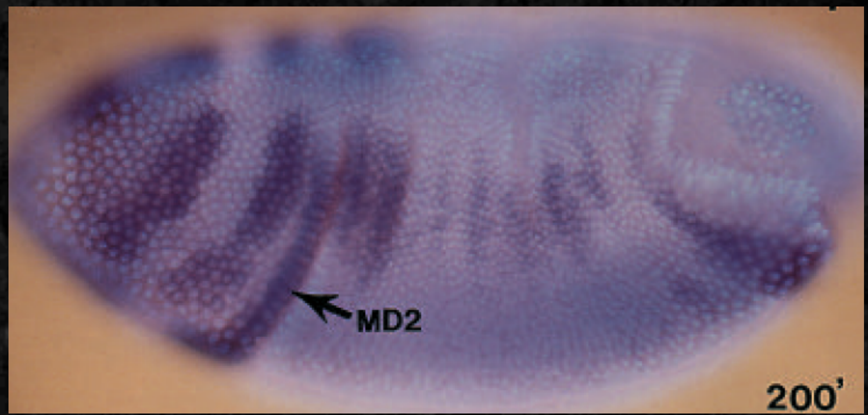
Morphogenesis

New transcription of Cdc25^{string} regulates the time of mitosis 14

Defers the question - what times transcription?

What about the first 13 cycles?



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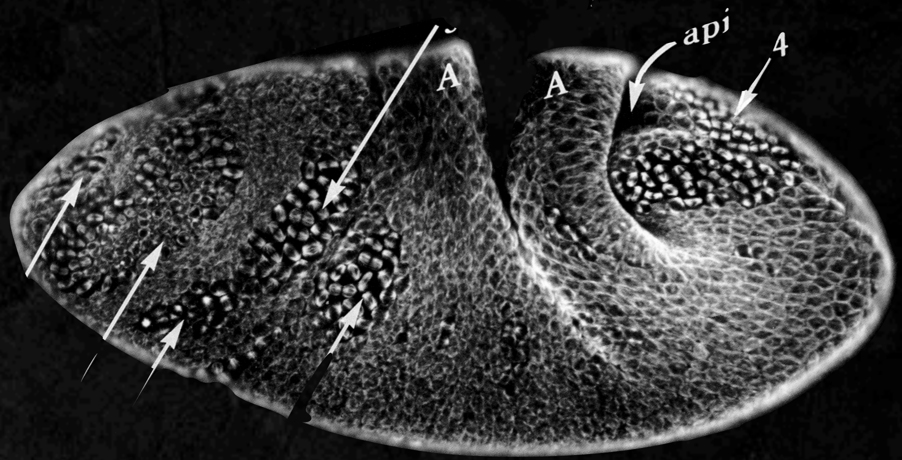

Mitosis 14

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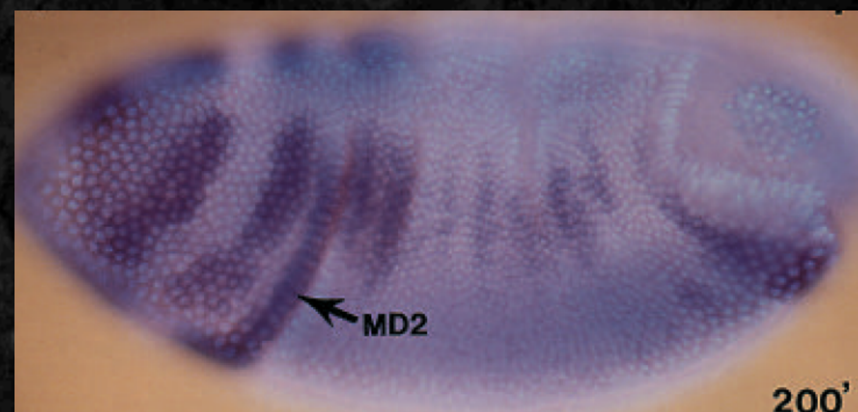

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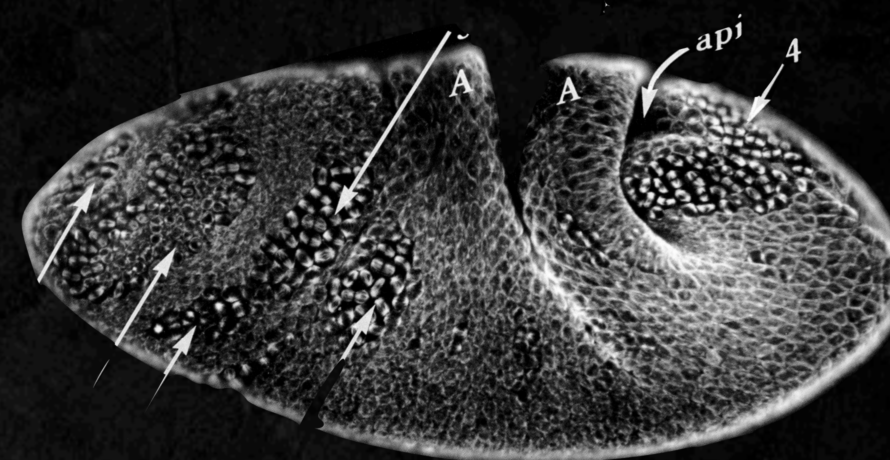
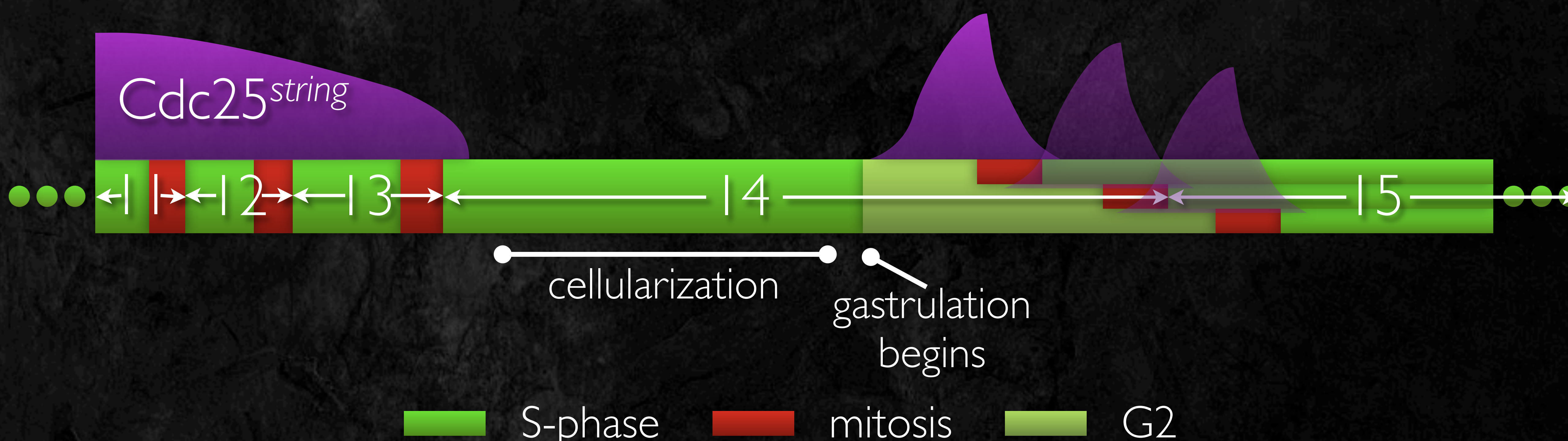


Mitosis 14



Maternal Cdc25*string* runs the early cycles

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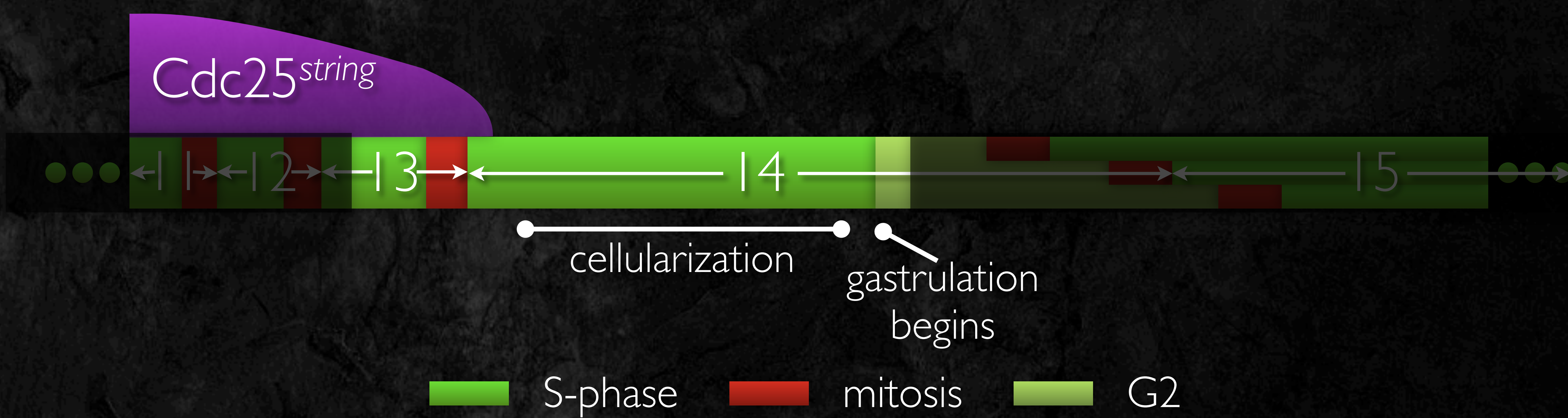

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Cell cycle Regulators Early

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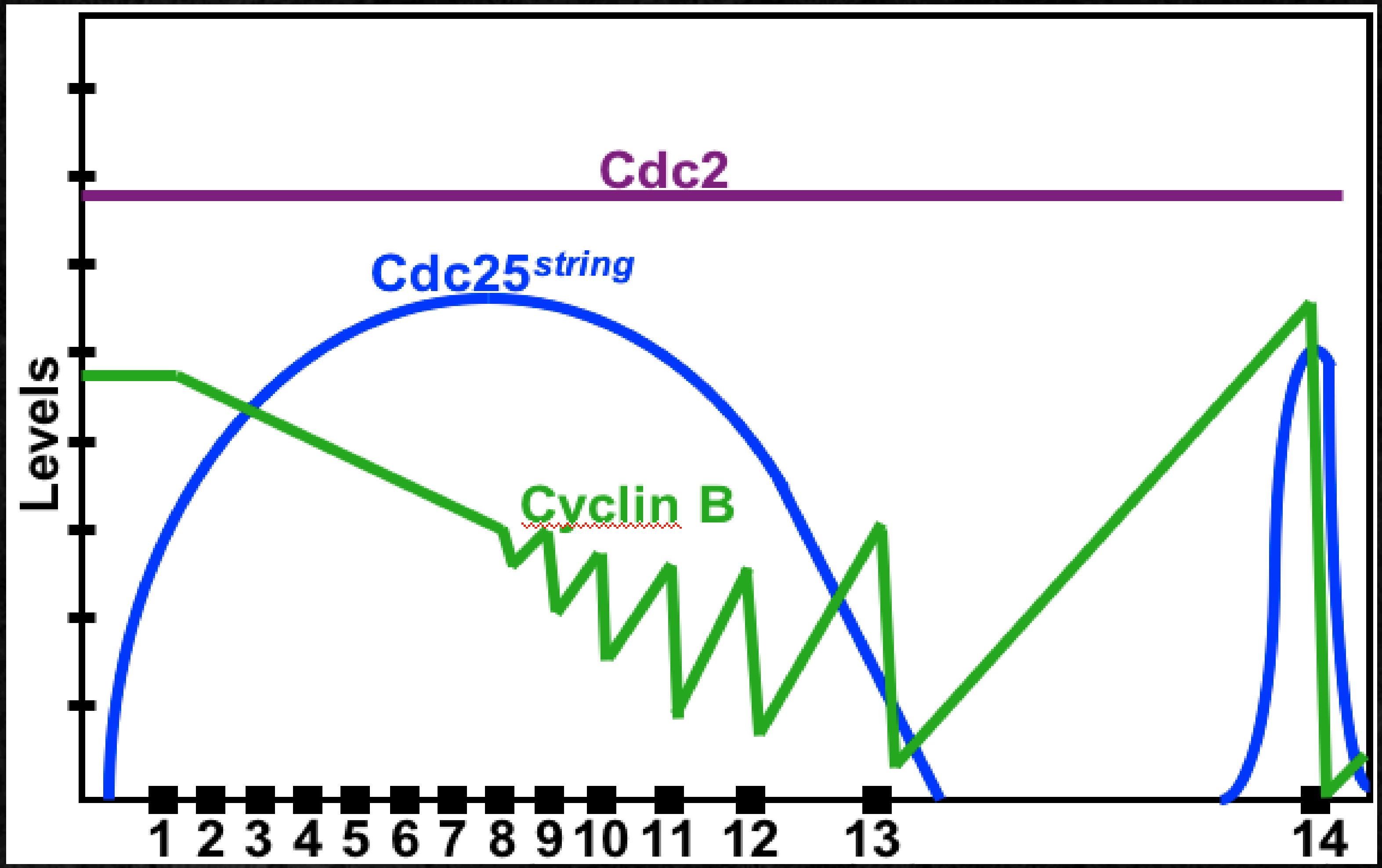
Single embryo Western blots



Time & Embryonic cell cycle #

Edgar et al., 1994

Cell cycle Regulators Early

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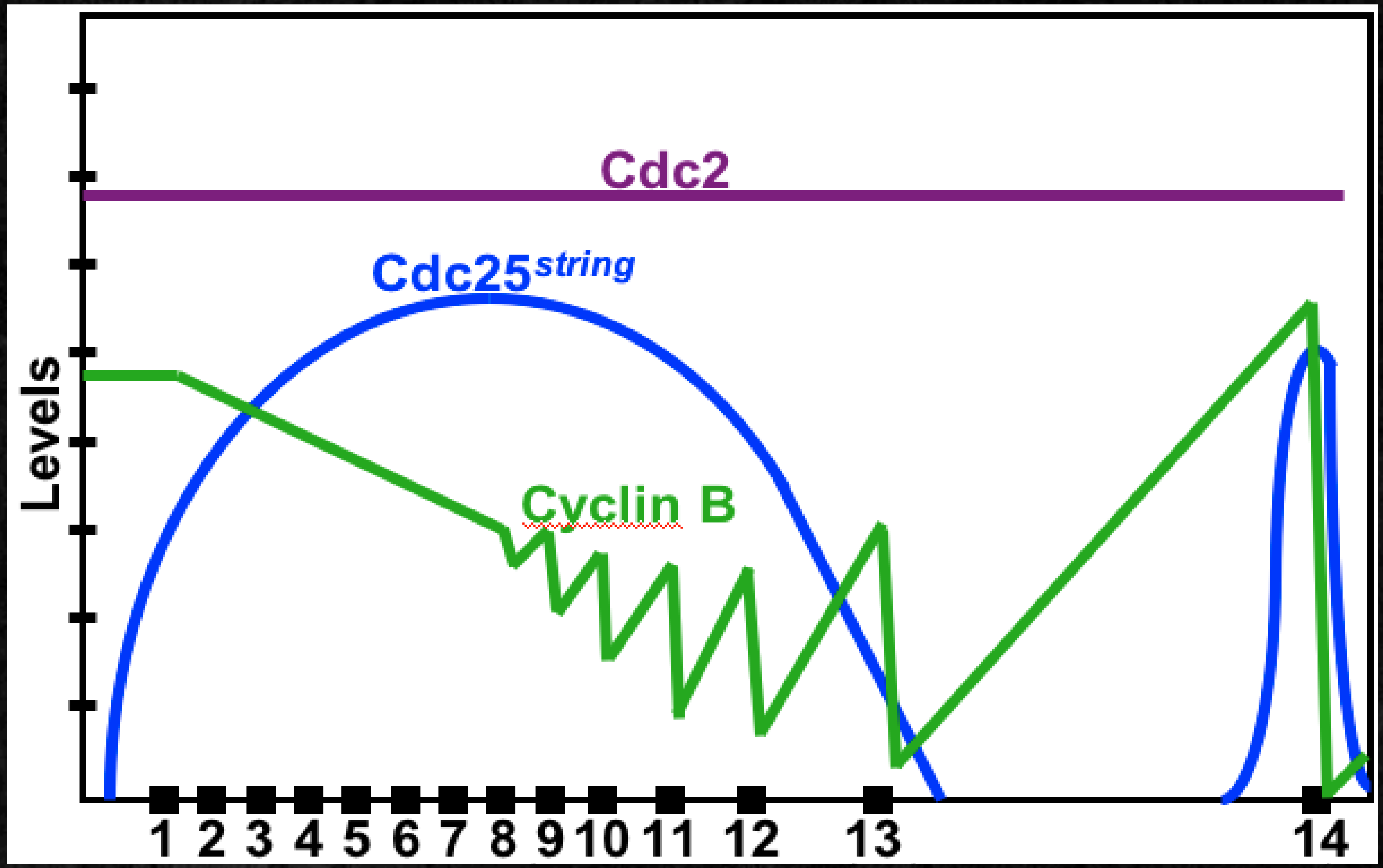

Time & Embryonic cell cycle #

No cyclin oscillation

Edgar et al., 1994

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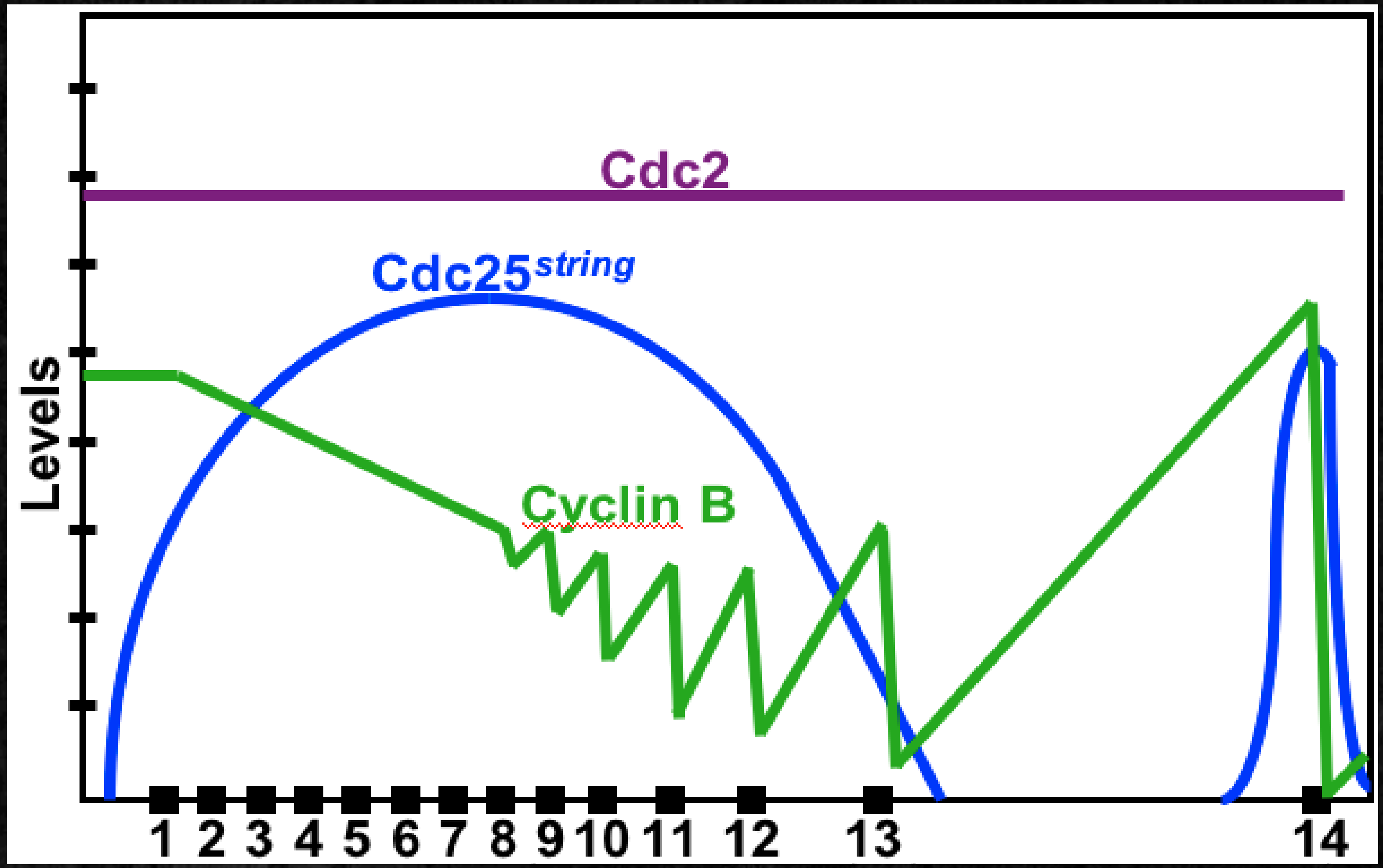

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No cyclin oscillation

Incomplete mitotic destruction

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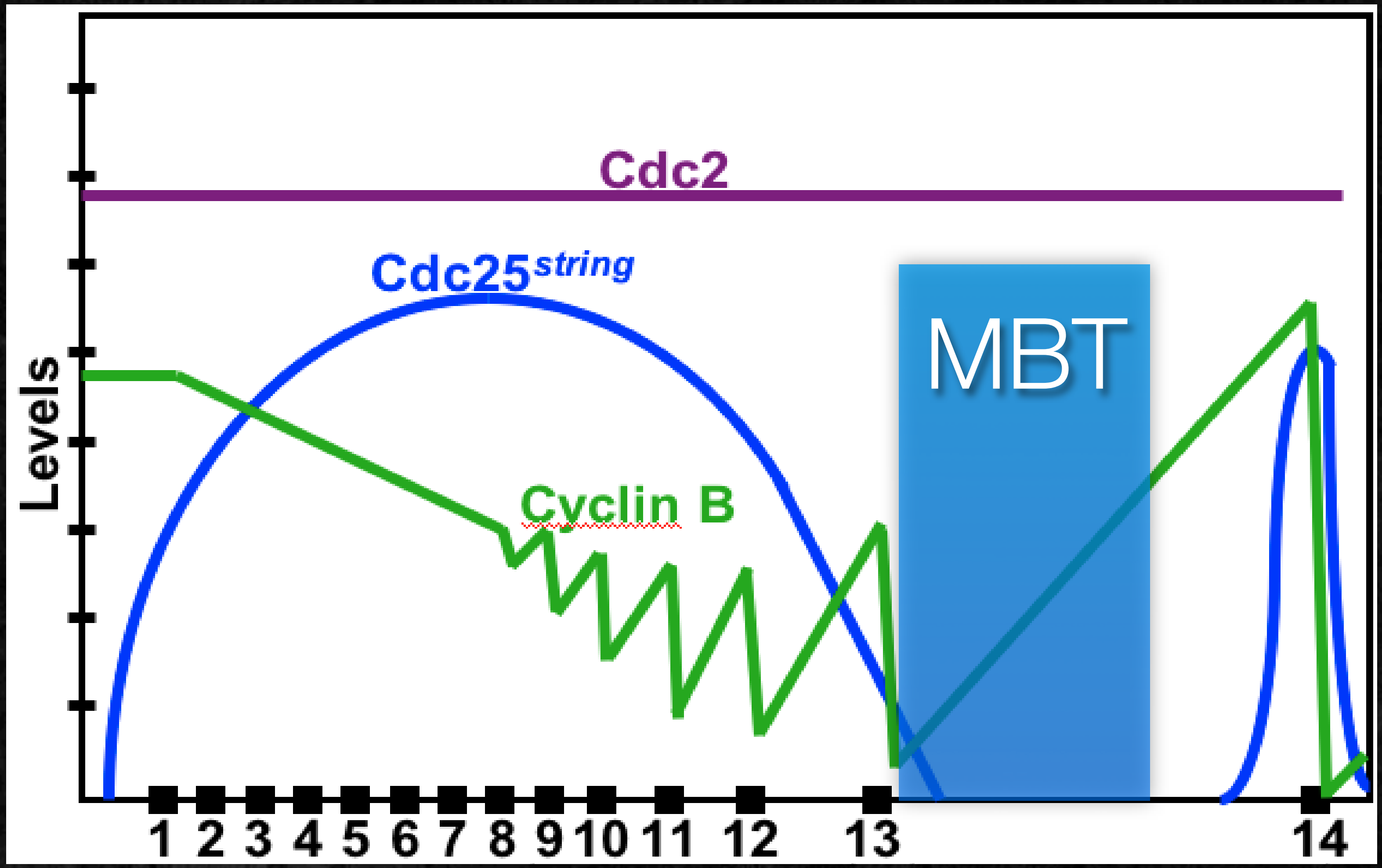

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Mitotic Cyclins

3 cyclins complex Cdk1 promote mitosis

	Mutant Phenotype	Double mutants
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Cyclin B	Viable: sterile	
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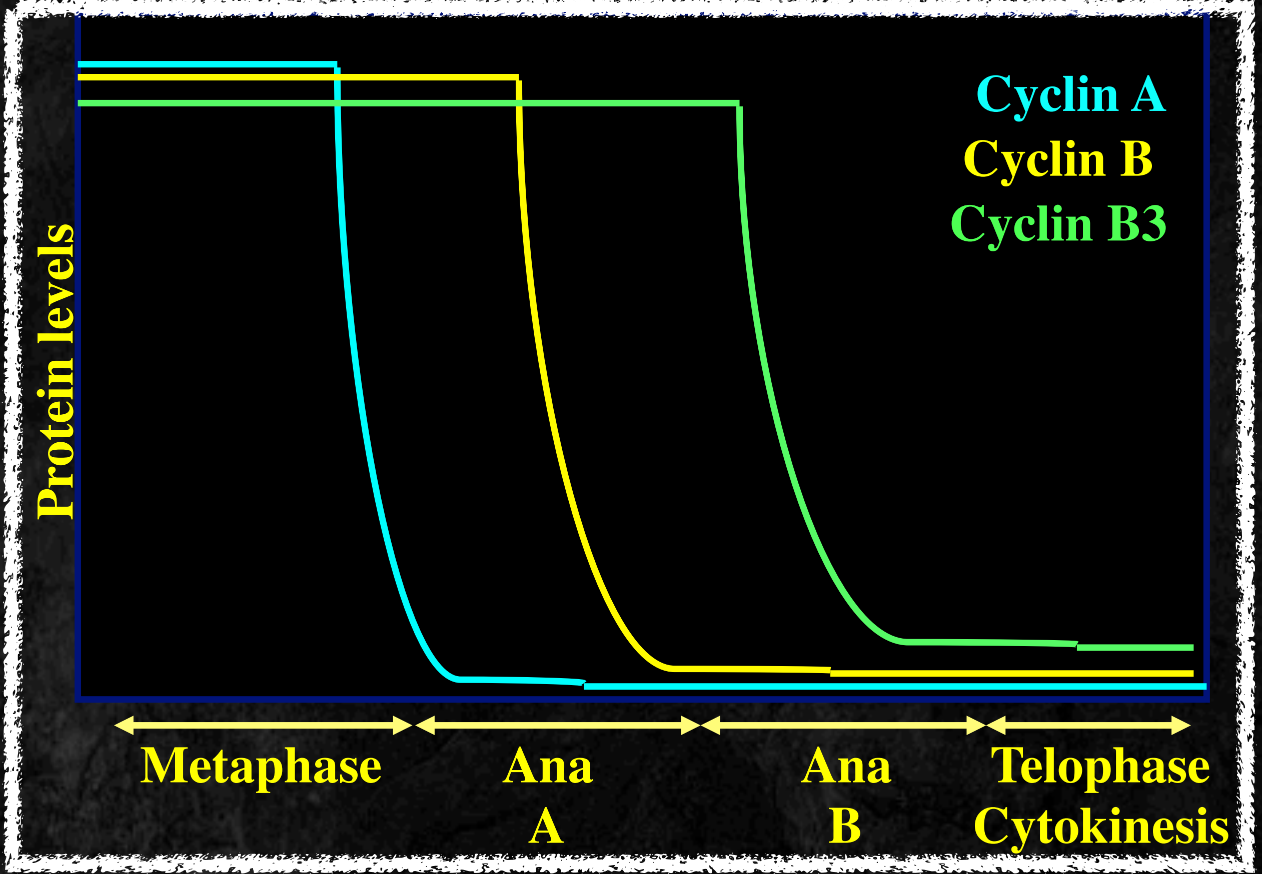
Sequential destruction in M



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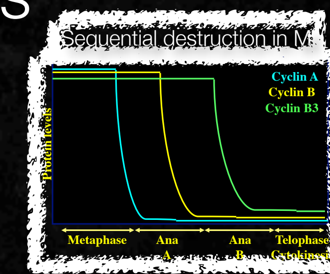
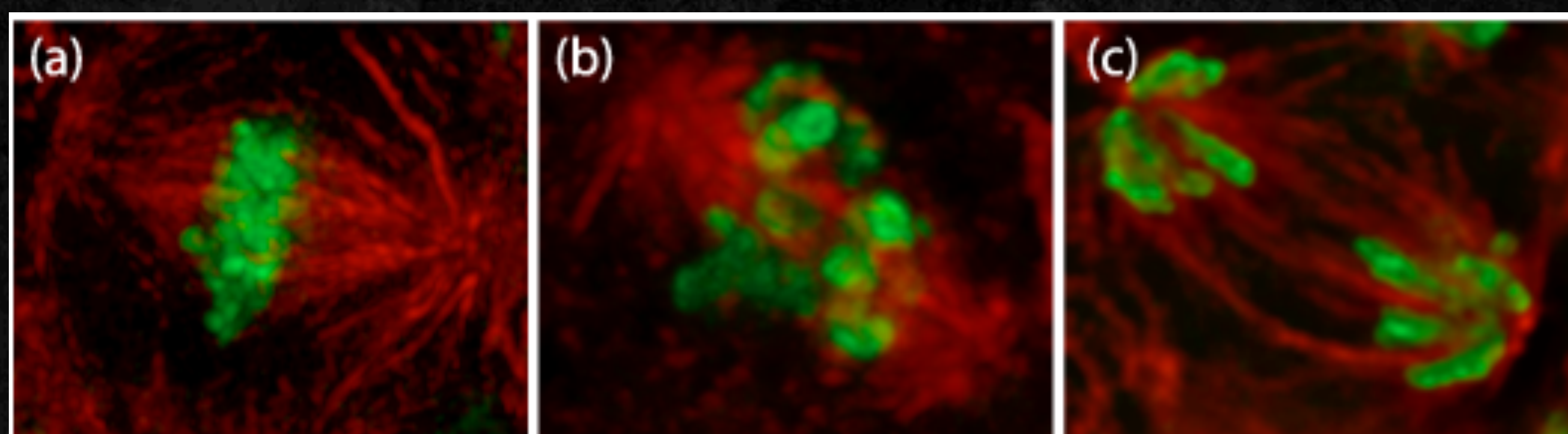


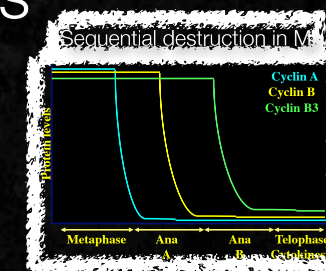
Sequential arrests by non-degradable cyclins



Cyclin A stable — Cyclin B stable — Cyclin B3 stable

Mitotic Cyclins

3 cyclins complex Cdk1 promote mitosis		Mutant Phenotype	Double mutants
	Cyclin A	Lethal (G2 cycle 16)	lethal with mitotic defects
	Cyclin B	Viable: sterile	
	Cyclin B3	Viable: female sterile	



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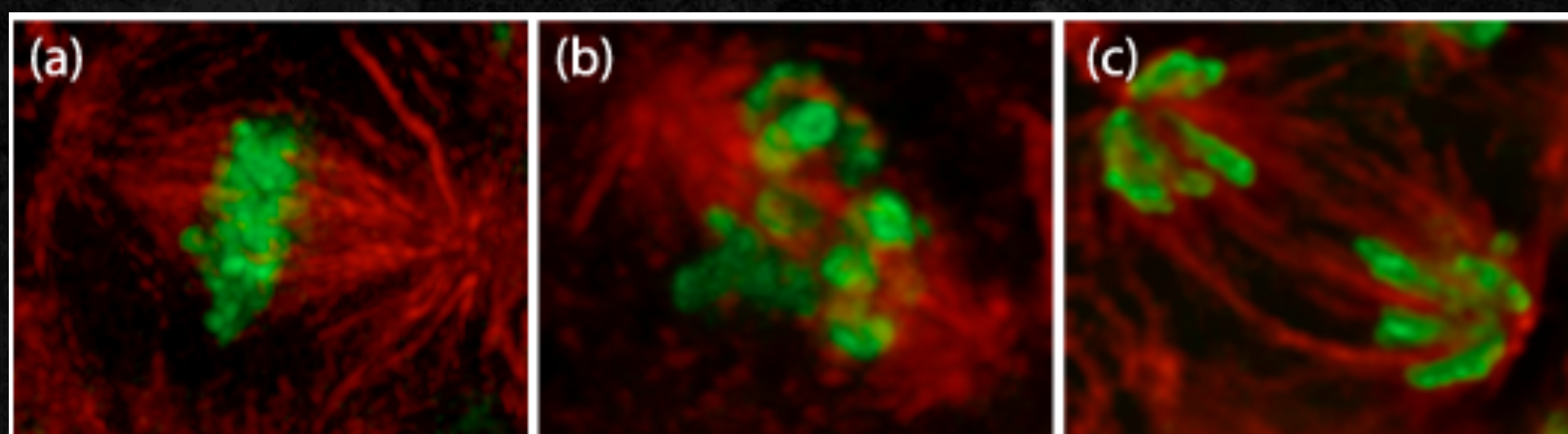
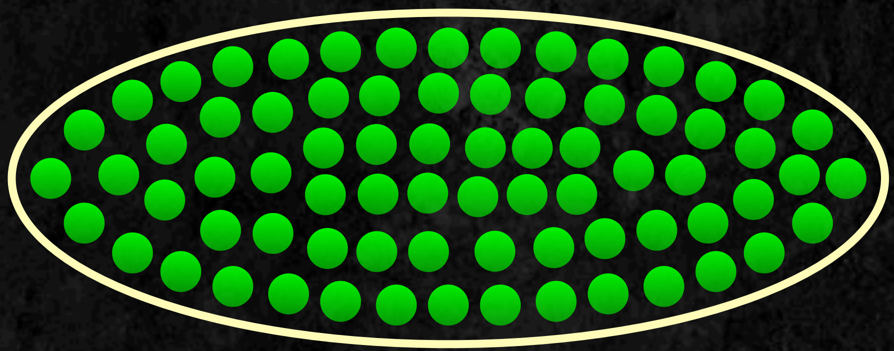


Cyclin A stable Cyclin B stable Cyclin B3 stable

In summary:
- 3 mitotic cyclins
- functions substantially overlap
- each with some specialization

RNAi Knockdown of Cyclins in Early Embryos



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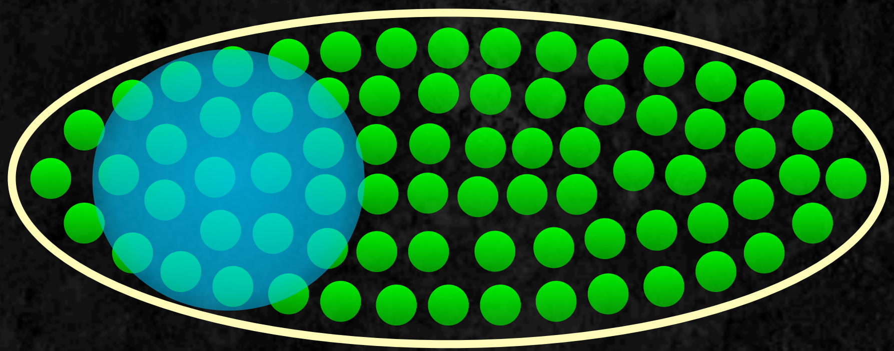

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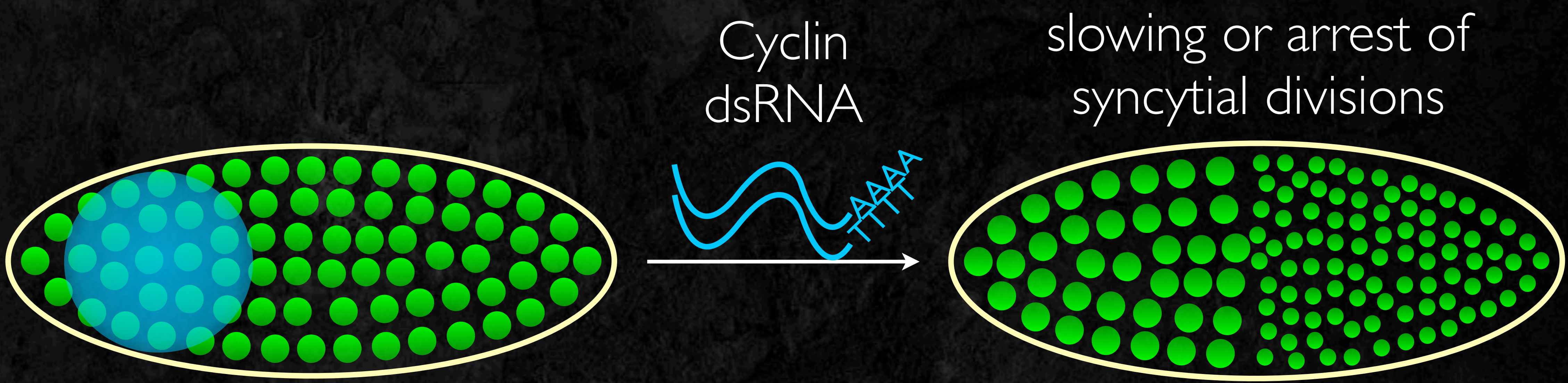

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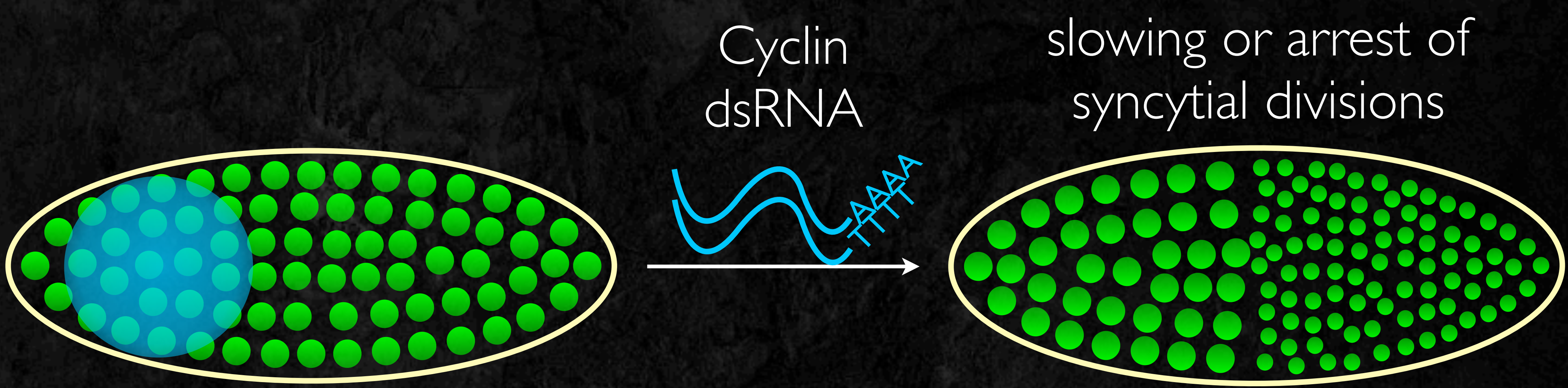
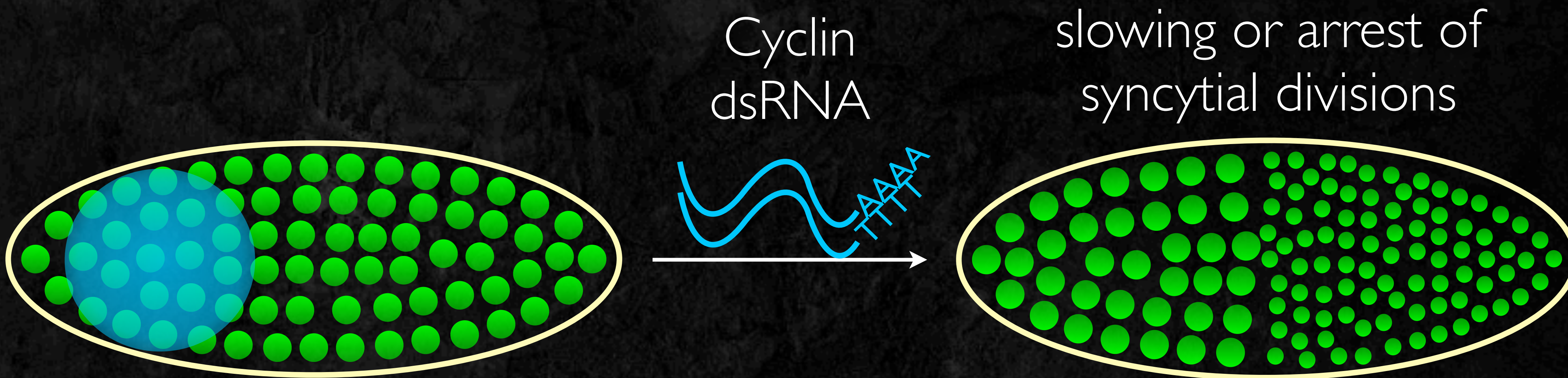


triple RNAi
(Cyc A/B/B3)
interphase
arrest

RNAi Knockdown of Cyclins in Early Embryos



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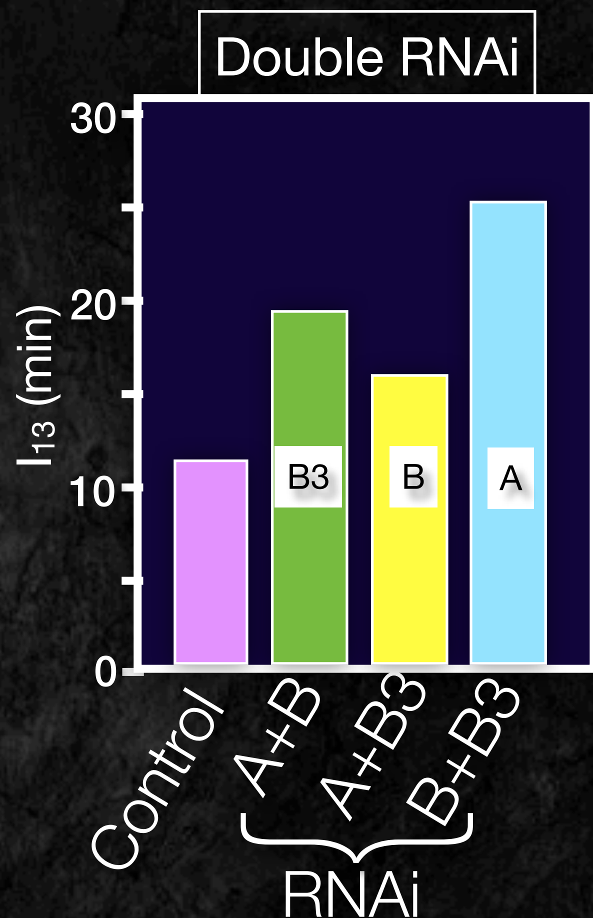
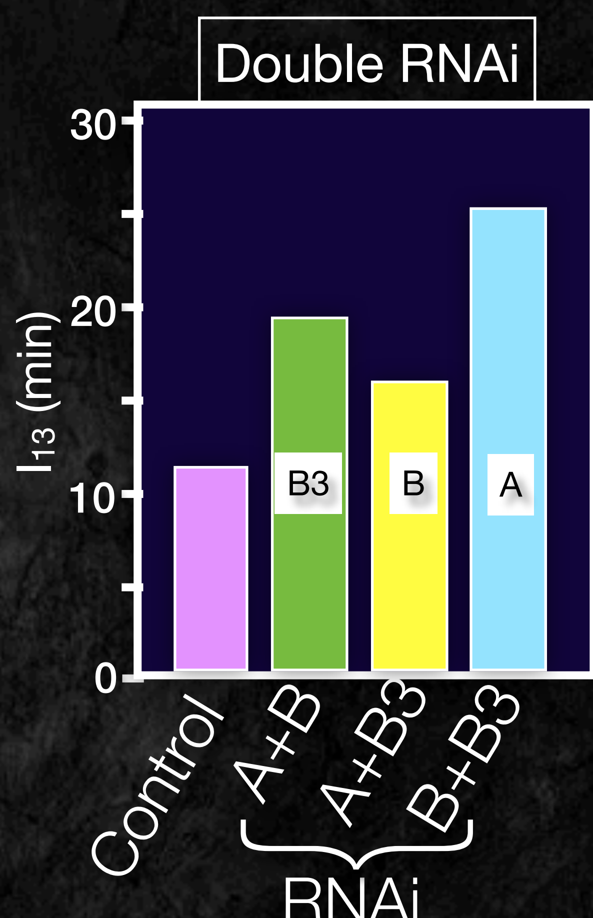


RNAi Knockdown of Cyclins in Early Embryos

Cyclin dsRNA

slowing or arrest of syncytial divisions

triple RNAi (Cyc A/B/B3) interphase arrest



Interphase length: influenced by level or type of cyclin

When there is one cyclin, does decrease in its level affect timing?

Mark McCleland

When there is one cyclin, does decrease in its level affect timing?

Knockdown A & B3

Mark McCleland

When there is one cyclin, does decrease in its level affect timing?

Knockdown A & B3

diploid 2 cyclin B genes

Mark McCleland

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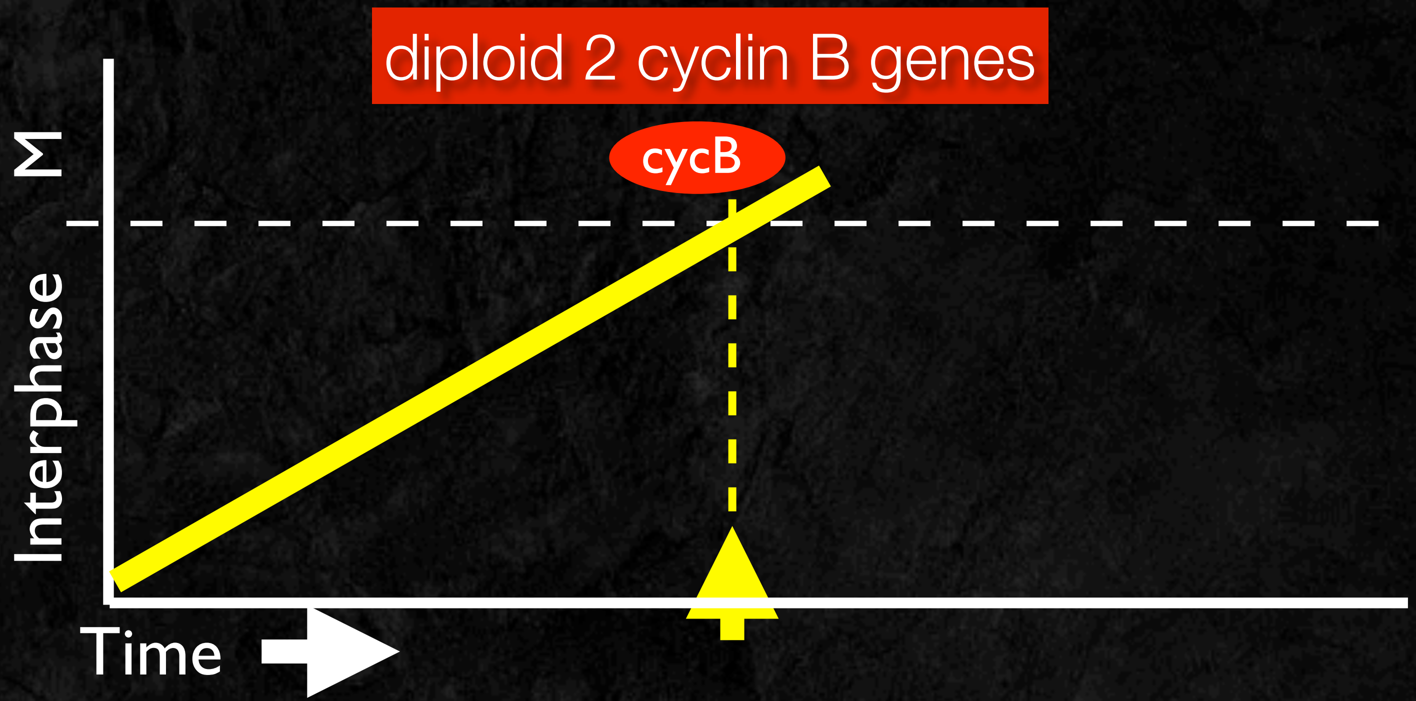

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What if there was only 1 copy?

Knockdown A & B3

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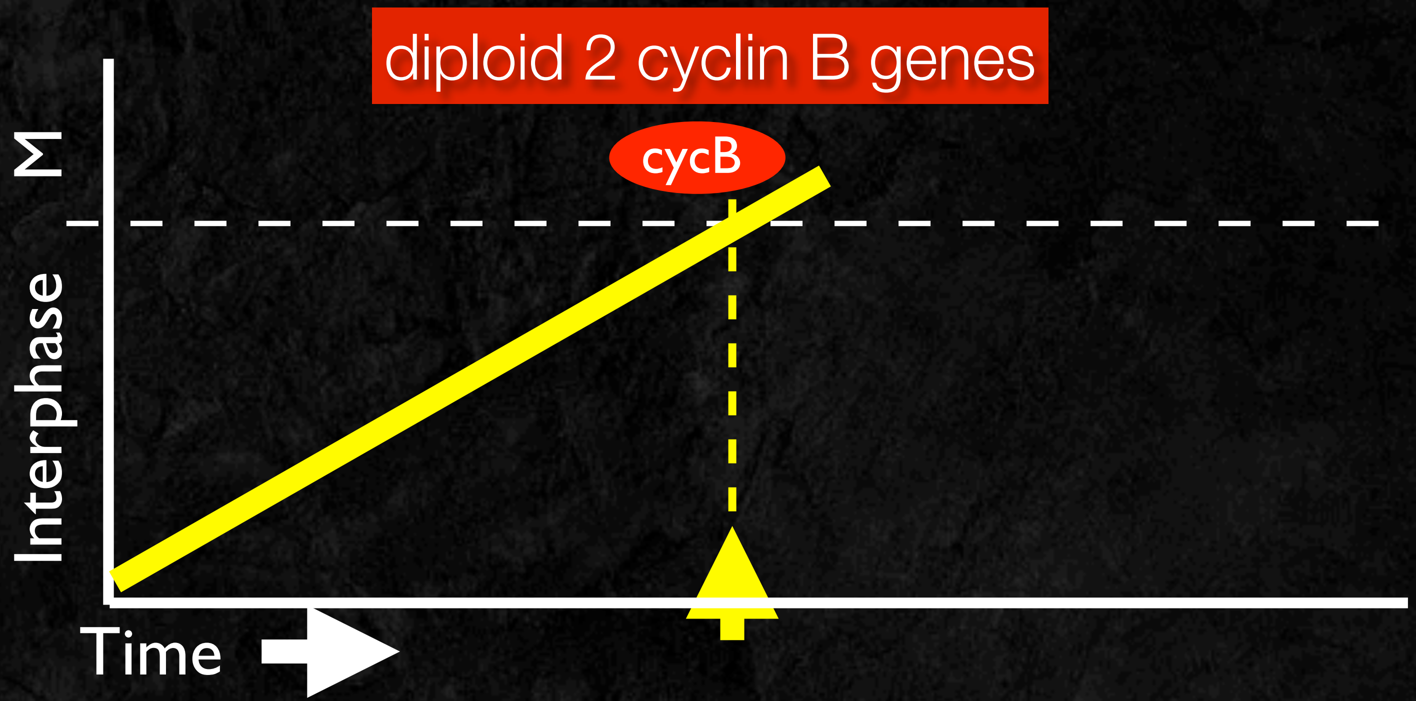

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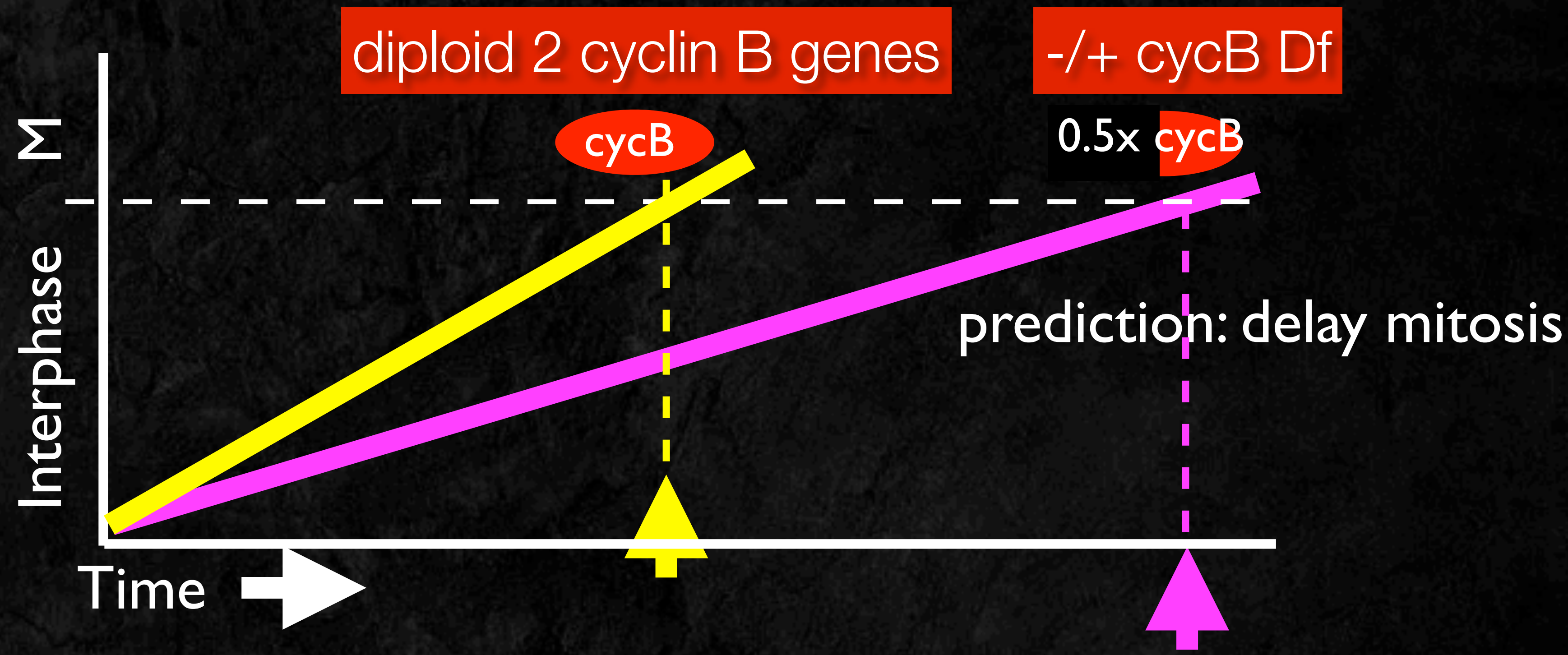

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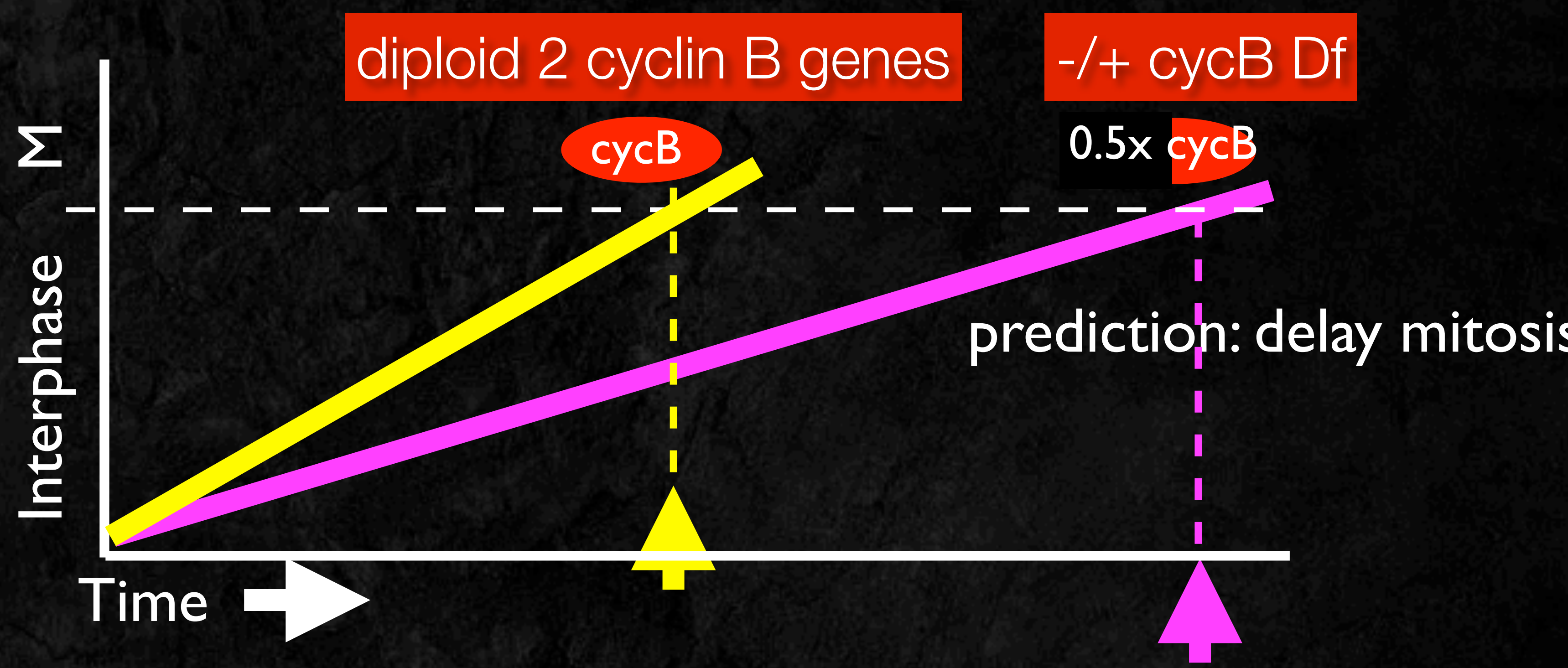
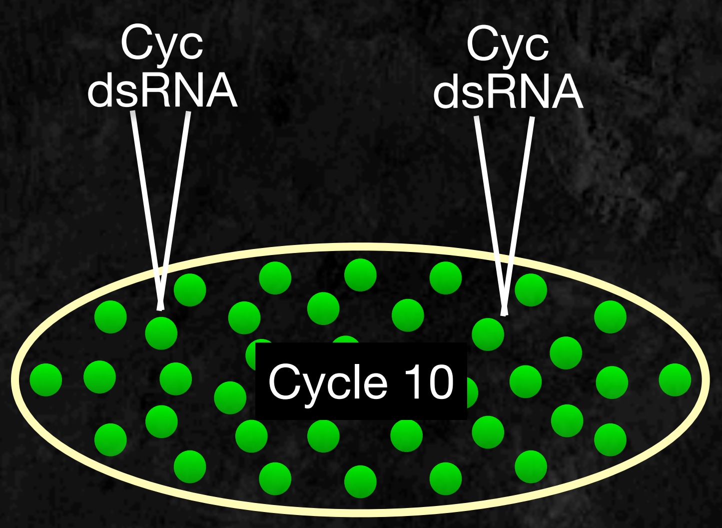


Finding

RNAi + gene dose: lowered cyclin synthesis to the point of mitotic failure without extending interphase

Can an increased level of cyclin B accelerate the cycle?



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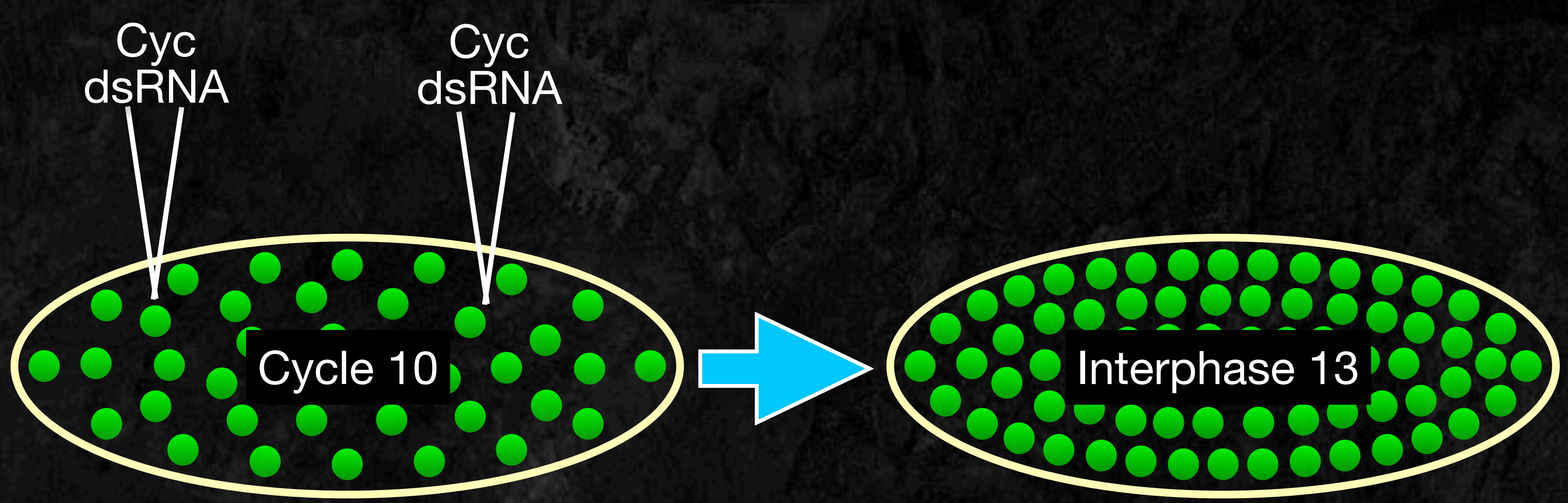

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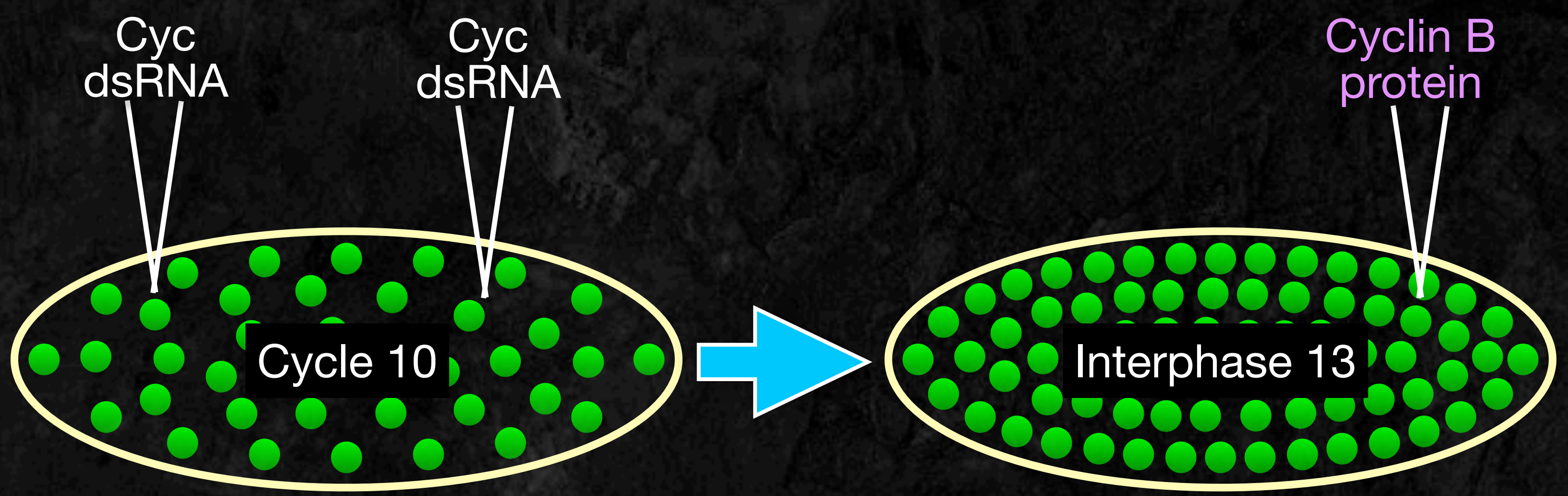

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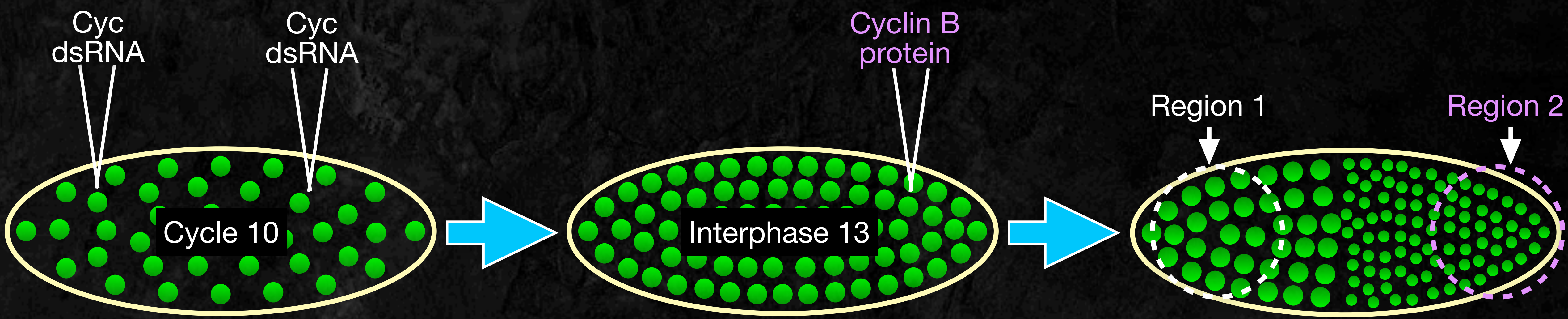

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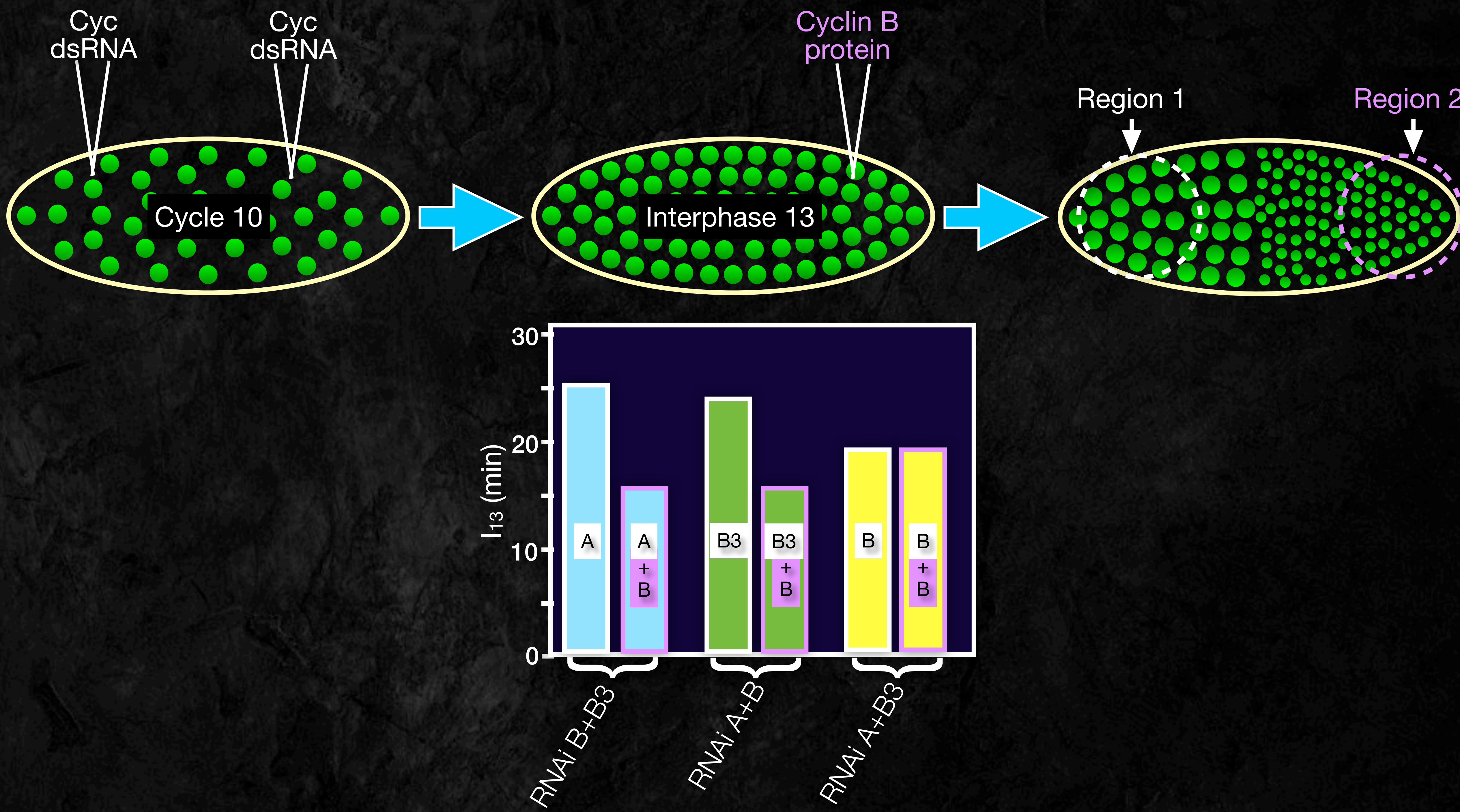

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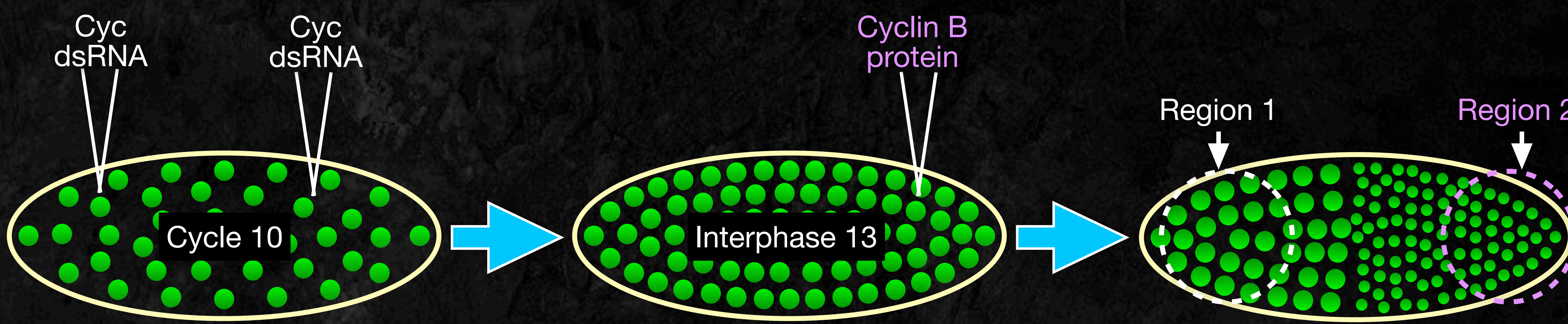
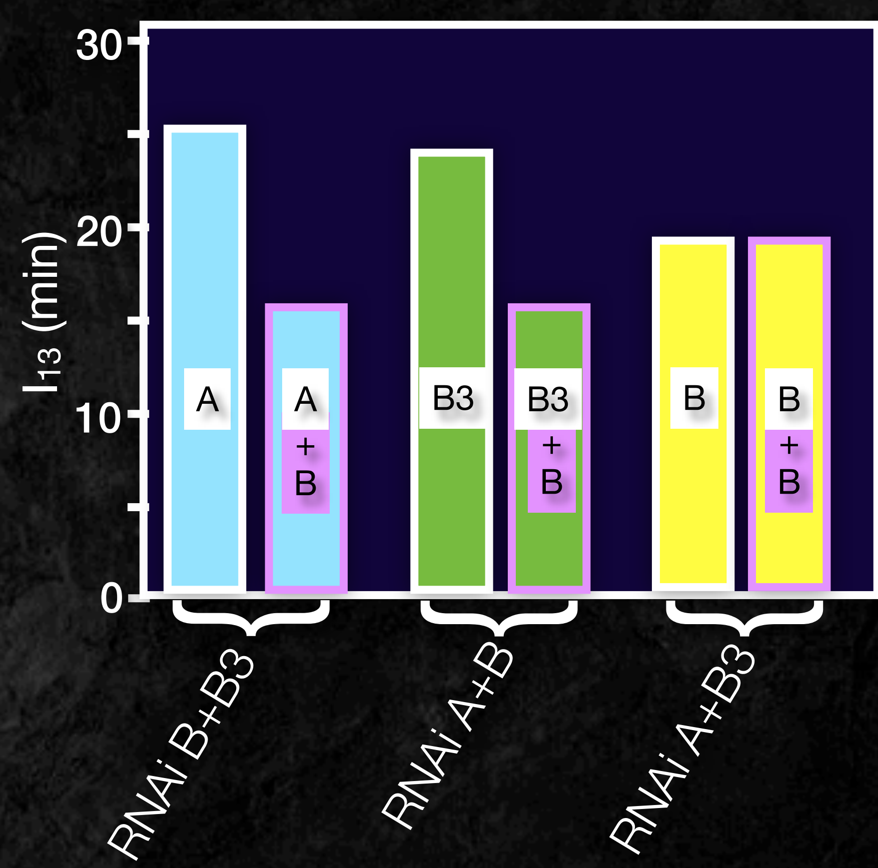


Increased type-diversity accelerates mitotic entry



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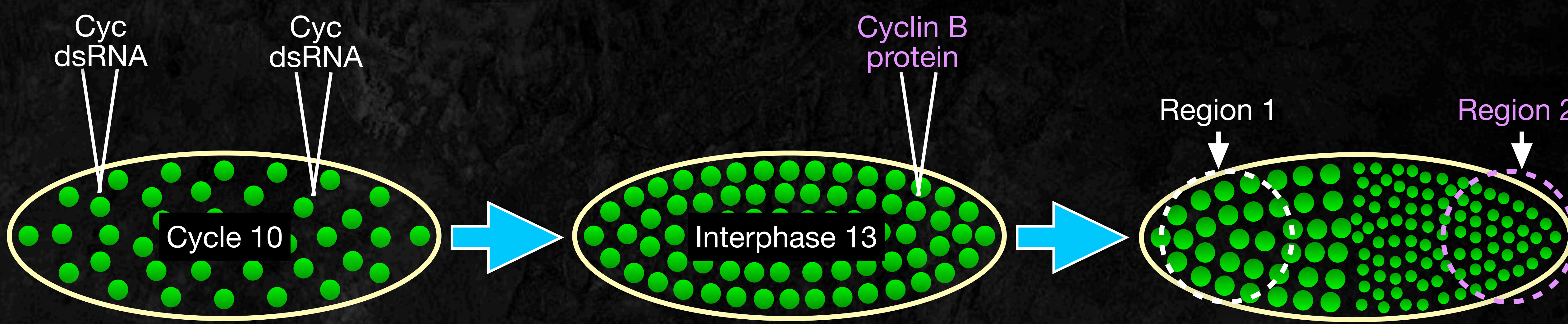

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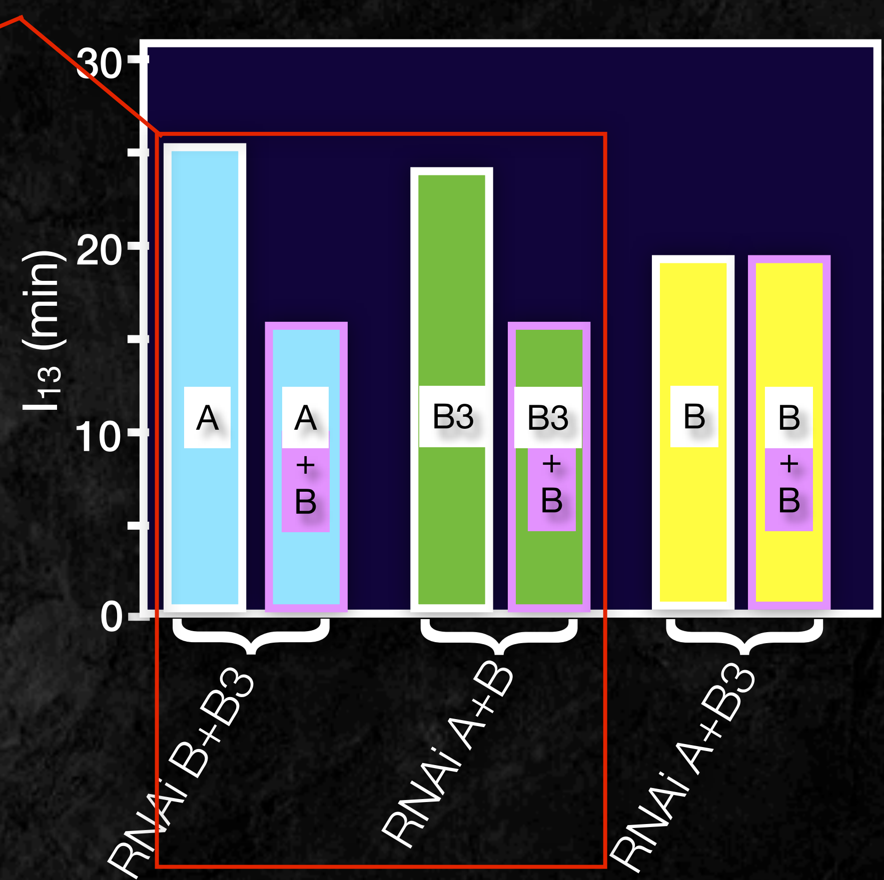
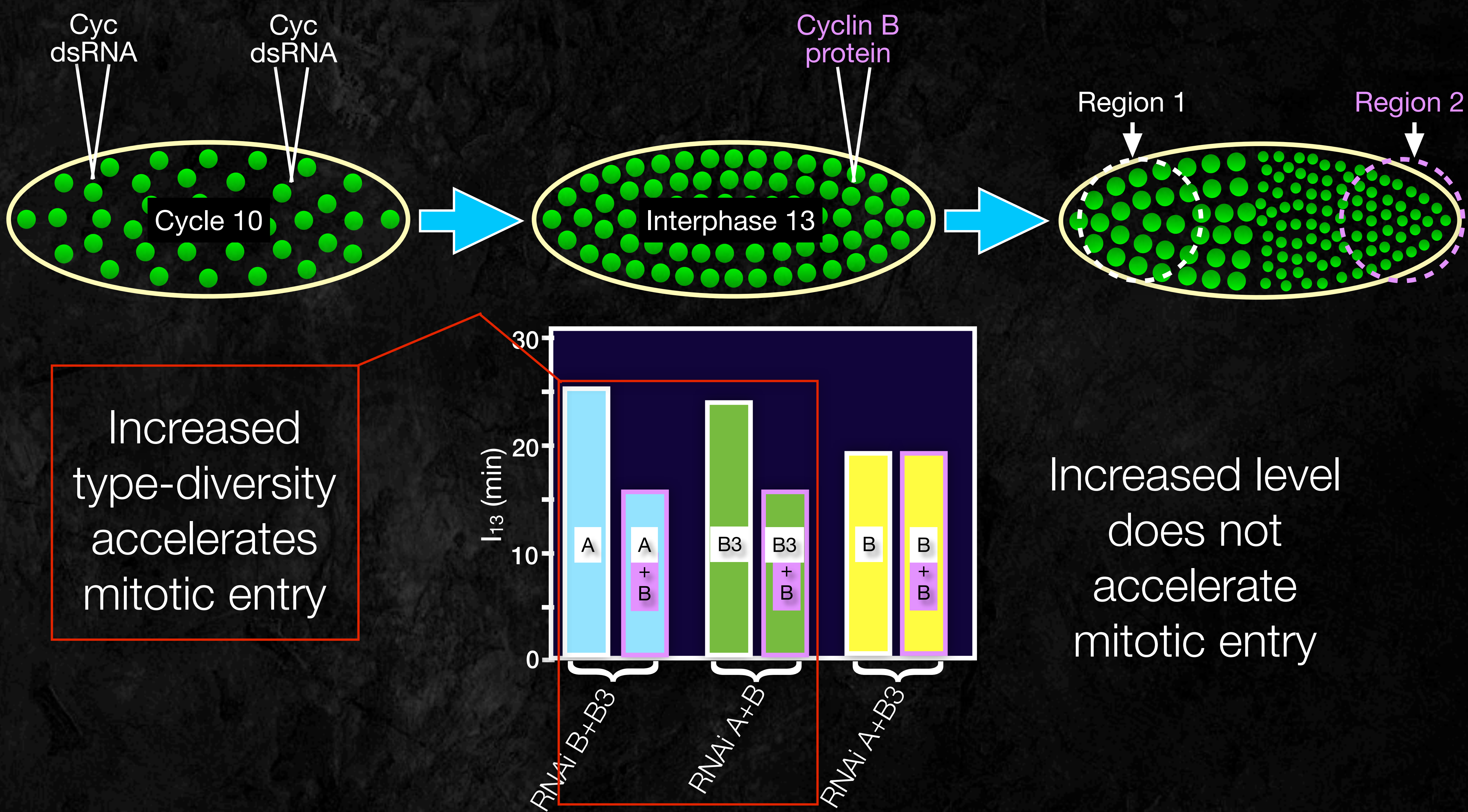


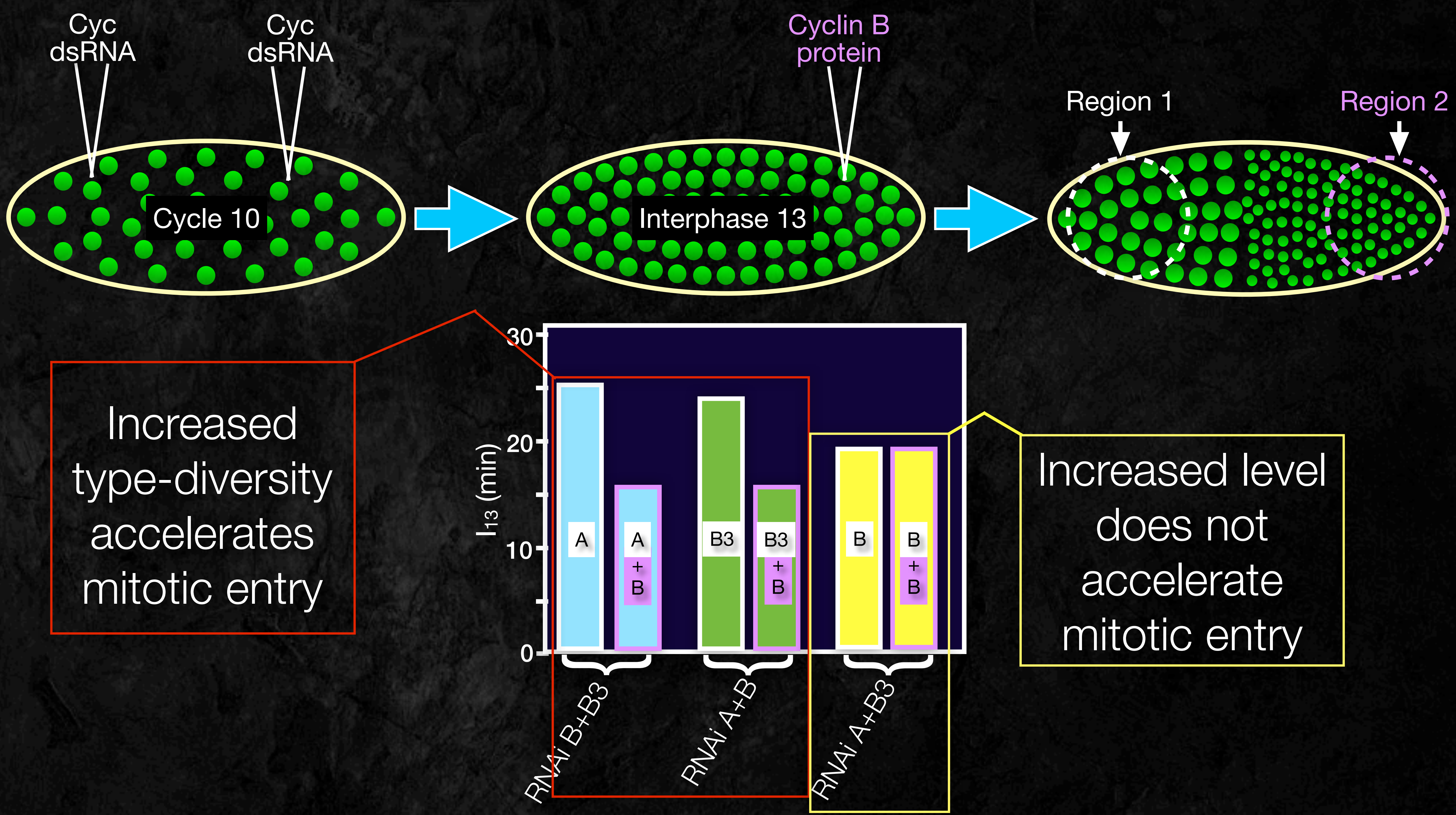
Can an increased level of cyclin B accelerate the cycle?



Increased type-diversity accelerates mitotic entry

Increased level does not accelerate mitotic entry

Can an increased level of cyclin B accelerate the cycle?



Timer

Conclude

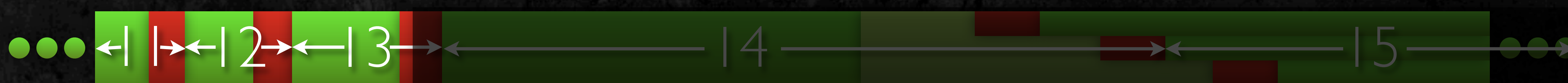
Accumulating level of cyclin does not time mitotic entry during the syncytial cycles.

Will return to influence of cyclin-type

Timer

Conclude

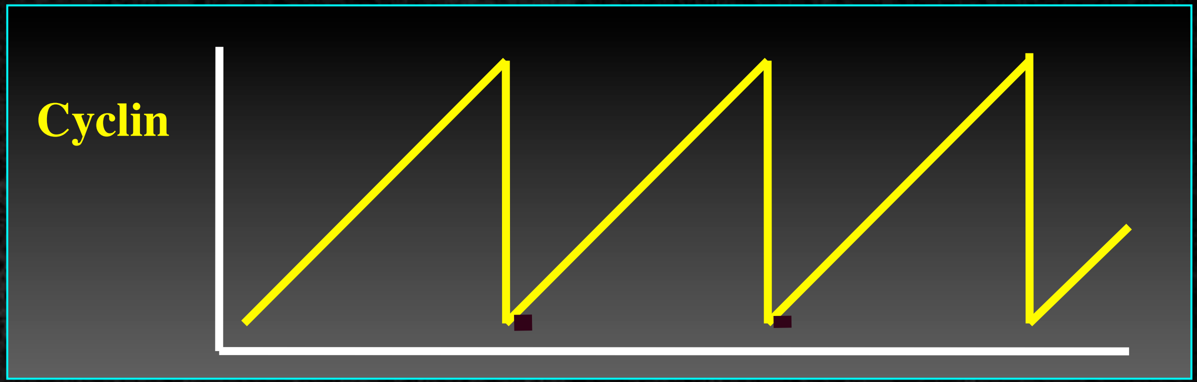
Accumulating level of cyclin does not time mitotic entry during the syncytial cycles.



Will return to influence of cyclin-type

A reteaching moment

A reteaching moment



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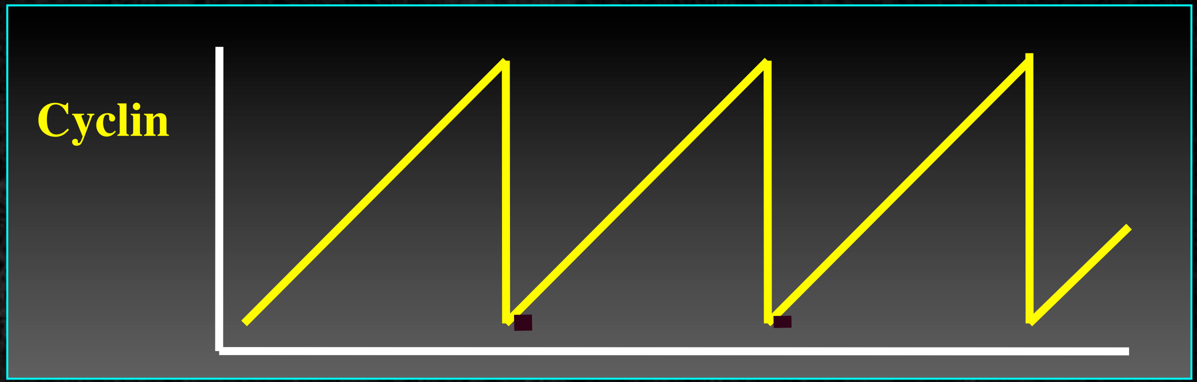

- Cyclin B accumulates to a threshold
- it triggers mitosis
- mitotic degradation resets the clock
- cyclins drive the cell cycle

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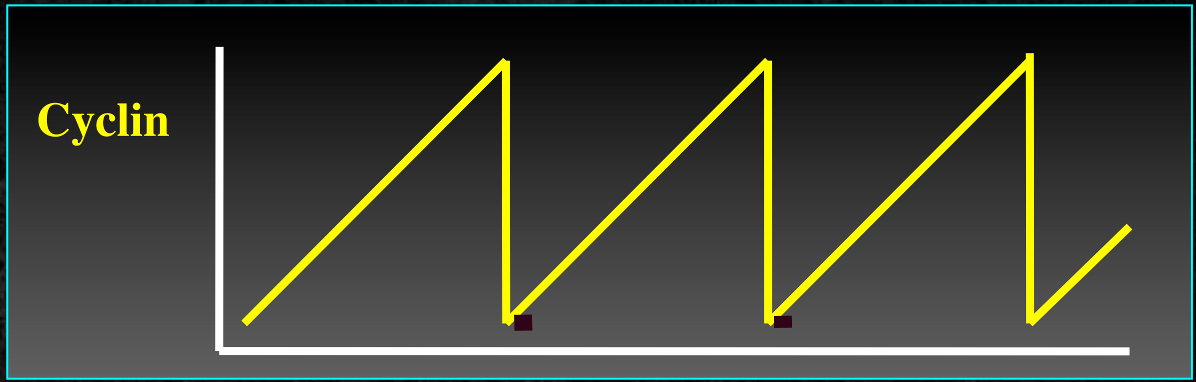

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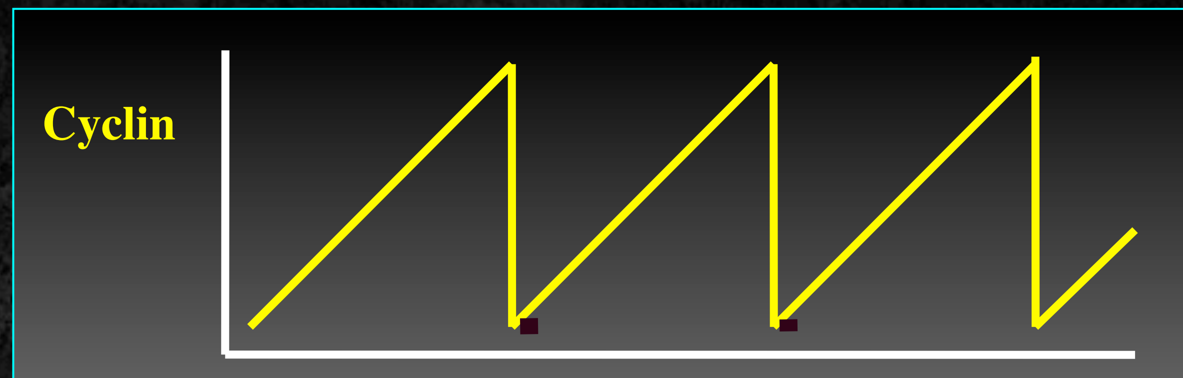

- Cyclin B accumulates in interphase
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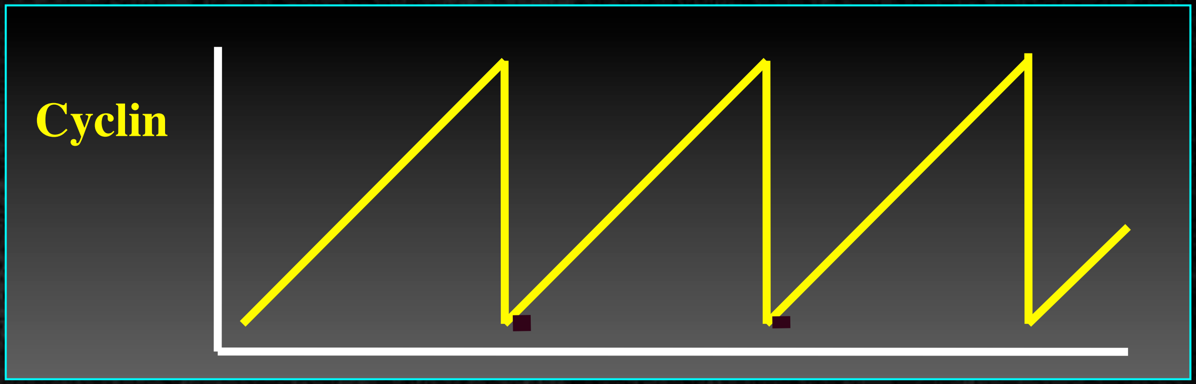
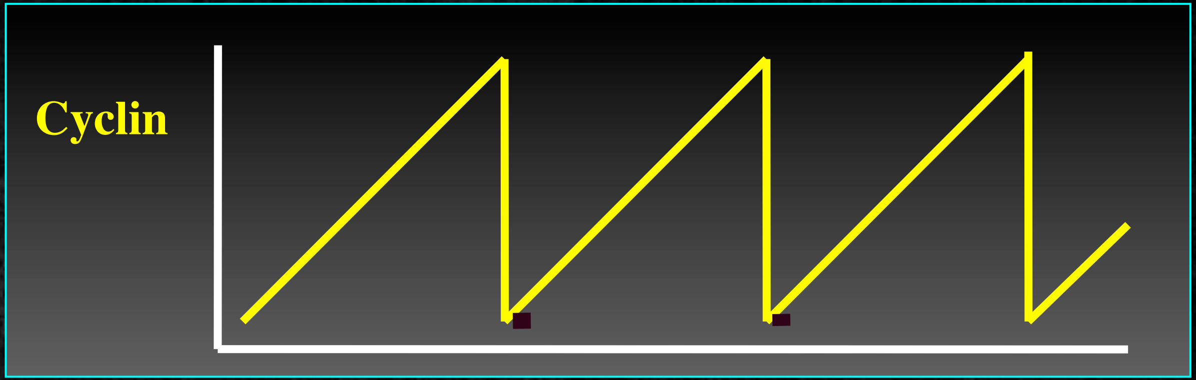


- Cyclin B accumulates in interphase
- cyclins are required for mitosis
- mitotic degradation resets the clock
- cyclins drive the cell cycle

A reteaching moment



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- mitotic cyclins are destroyed at mitosis
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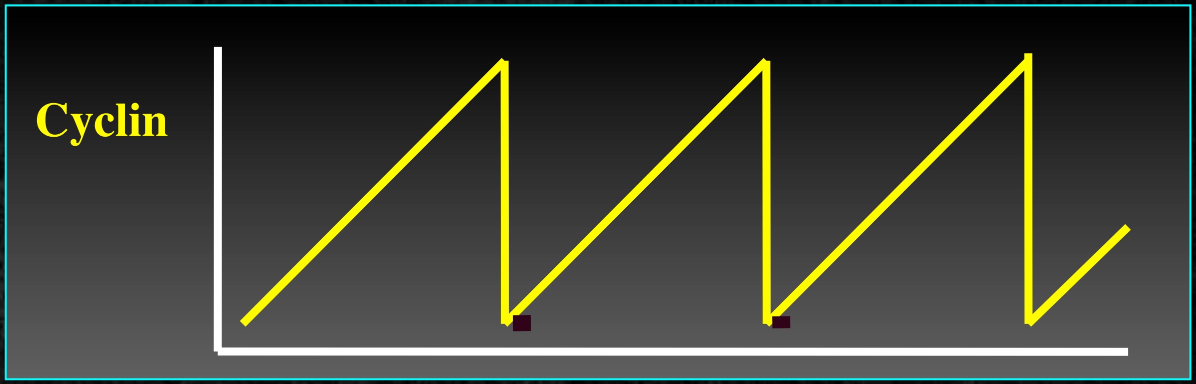

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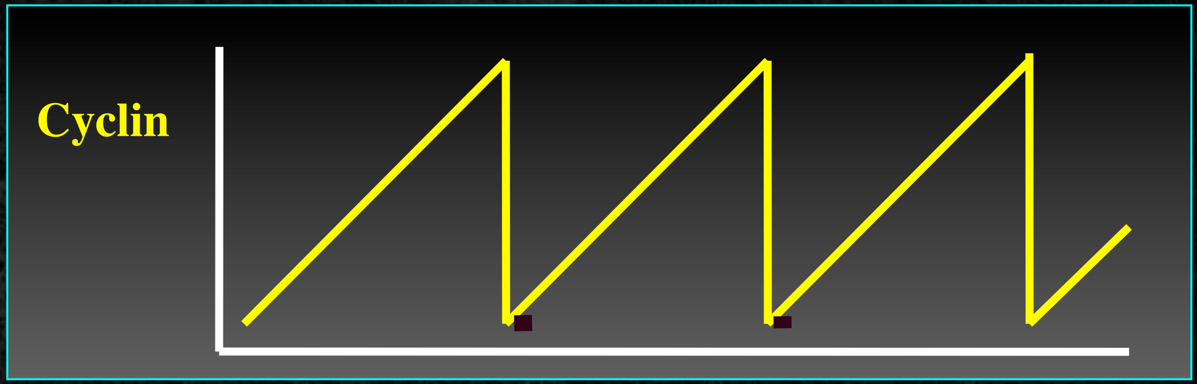

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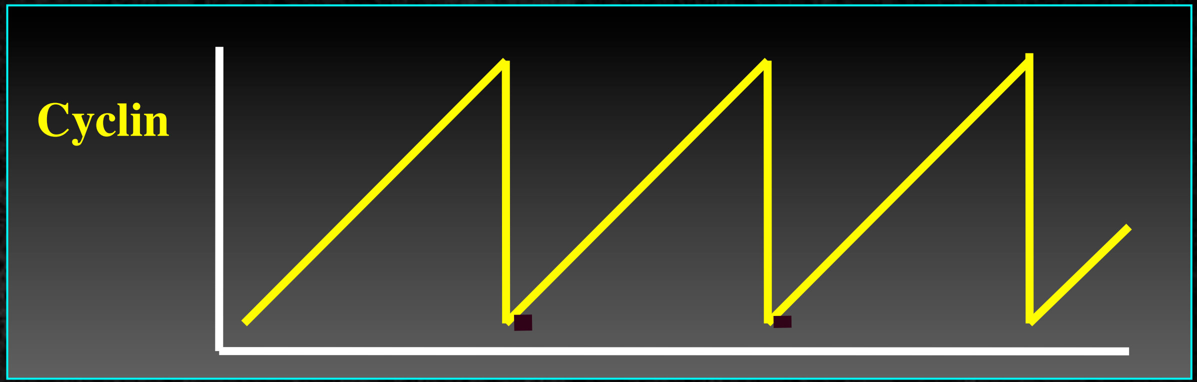

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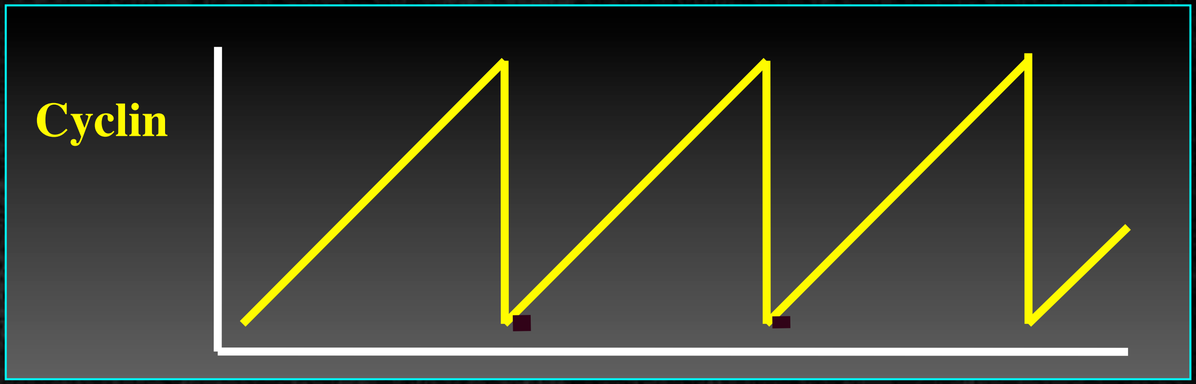
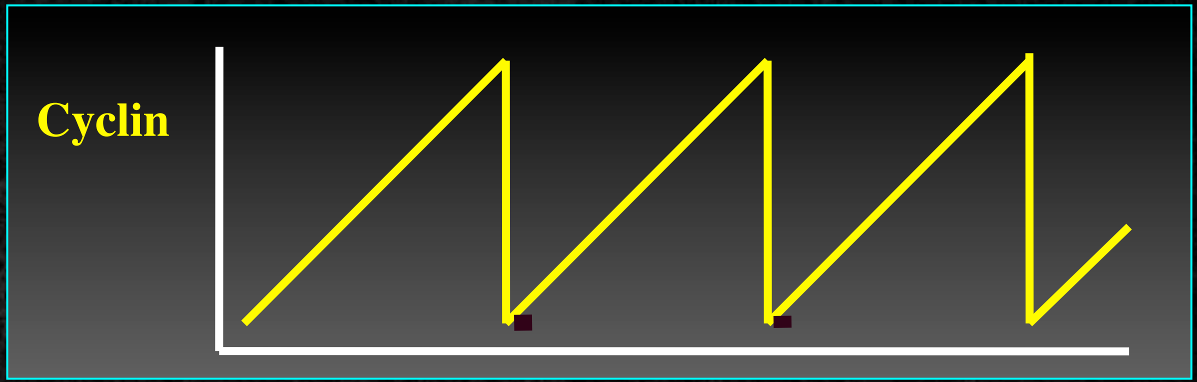


Water

A reteaching moment



Water

Required for the job

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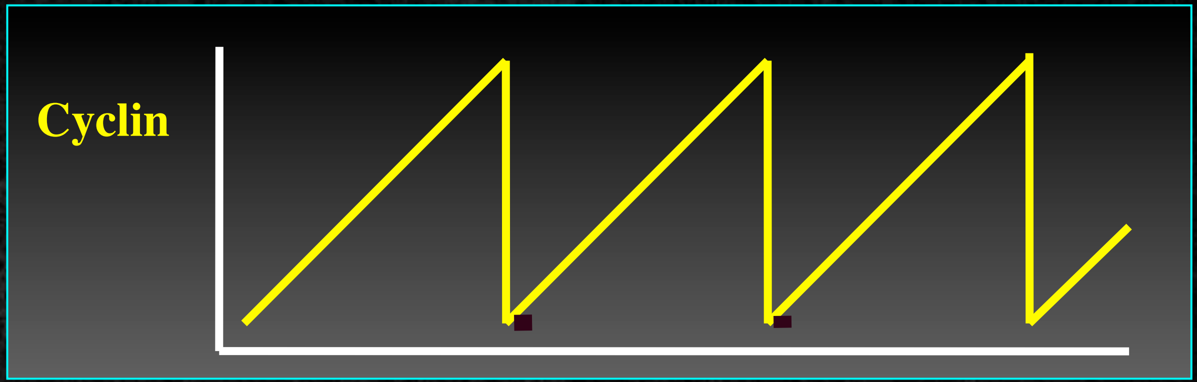
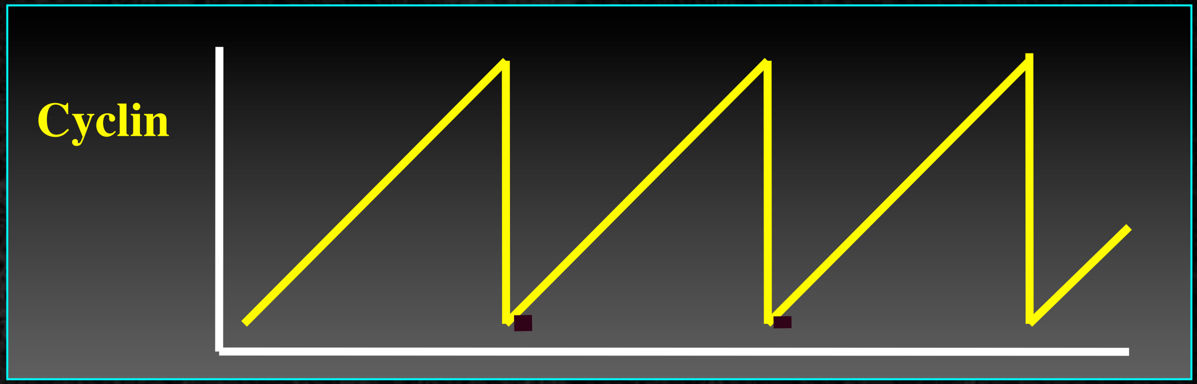


Water

Required for the job

Consumed in the process

A reteaching moment



Water

Required for the job

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Some re-accumulation required

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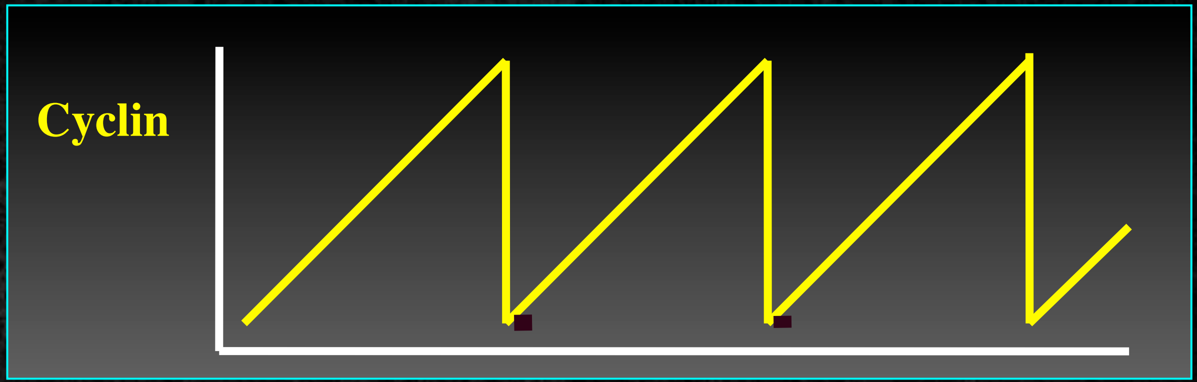

Water

Required for the job

Consumed in the process

Some re-accumulation required

If not Cyclin, what times M?

Early cycles - No gap phases
S phase must complete before M

Mitosis S-phase
S-phase

If not Cyclin, what times M?

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If not Cyclin, what times M?

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S phase must complete before M

Experiment - Delete S phase

If not Cyclin, what times M?

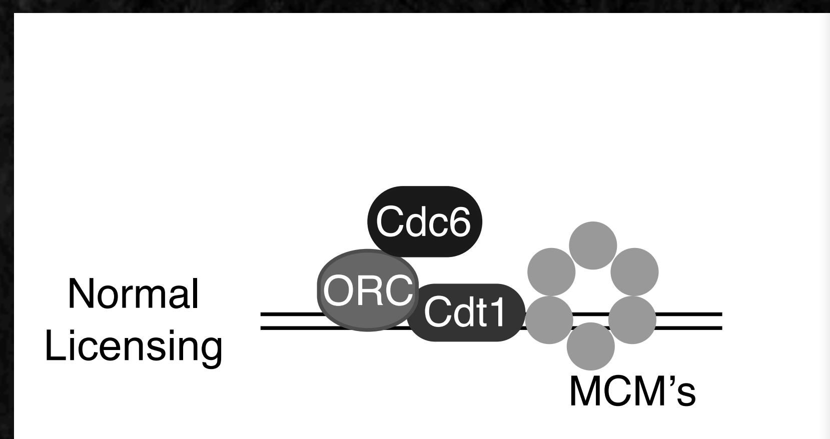
Early cycles - No gap phases
S phase must complete before M

Experiment - Delete S phase

What happens to interphase length?

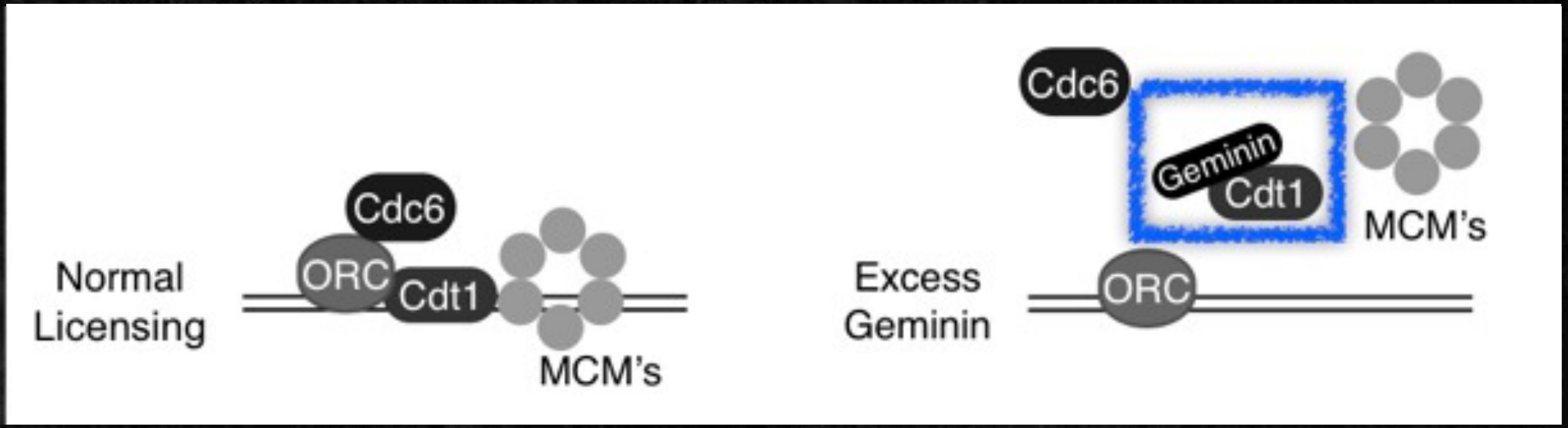
Deleting S phase

Licensing origin
for replication



Deleting S phase

Geminin blocks ori licensing



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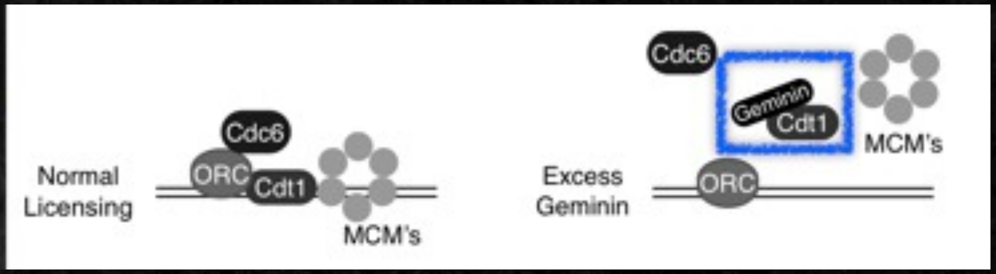

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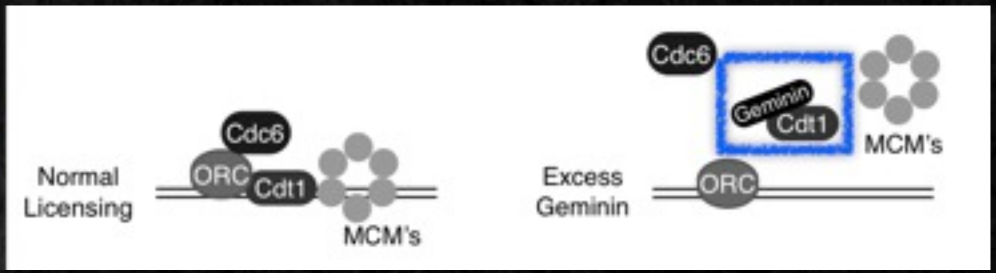

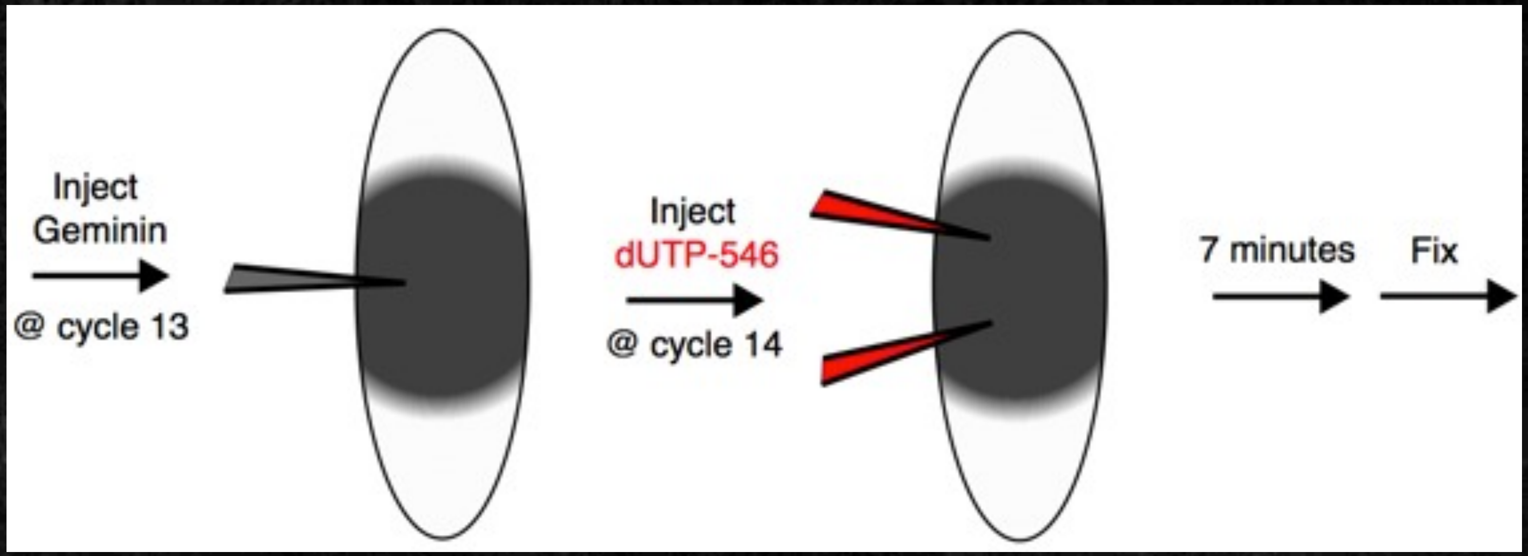

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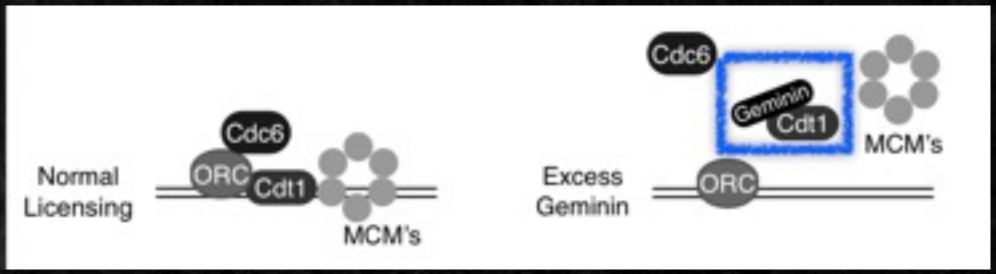

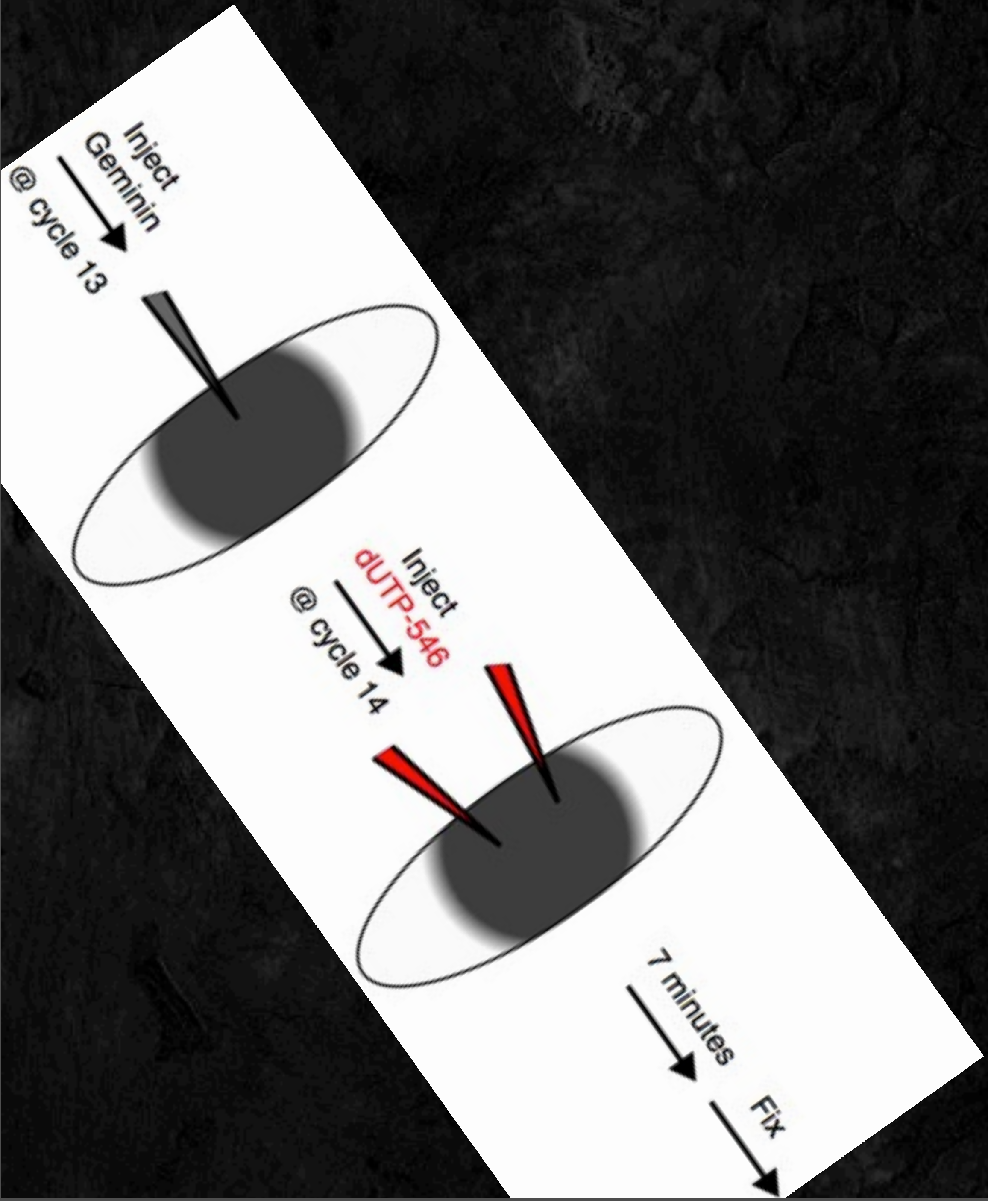

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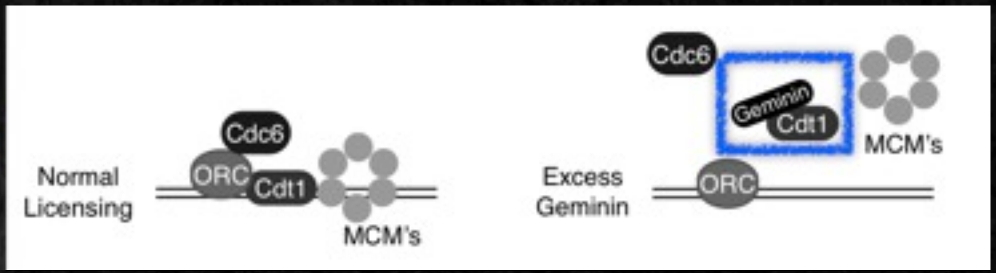
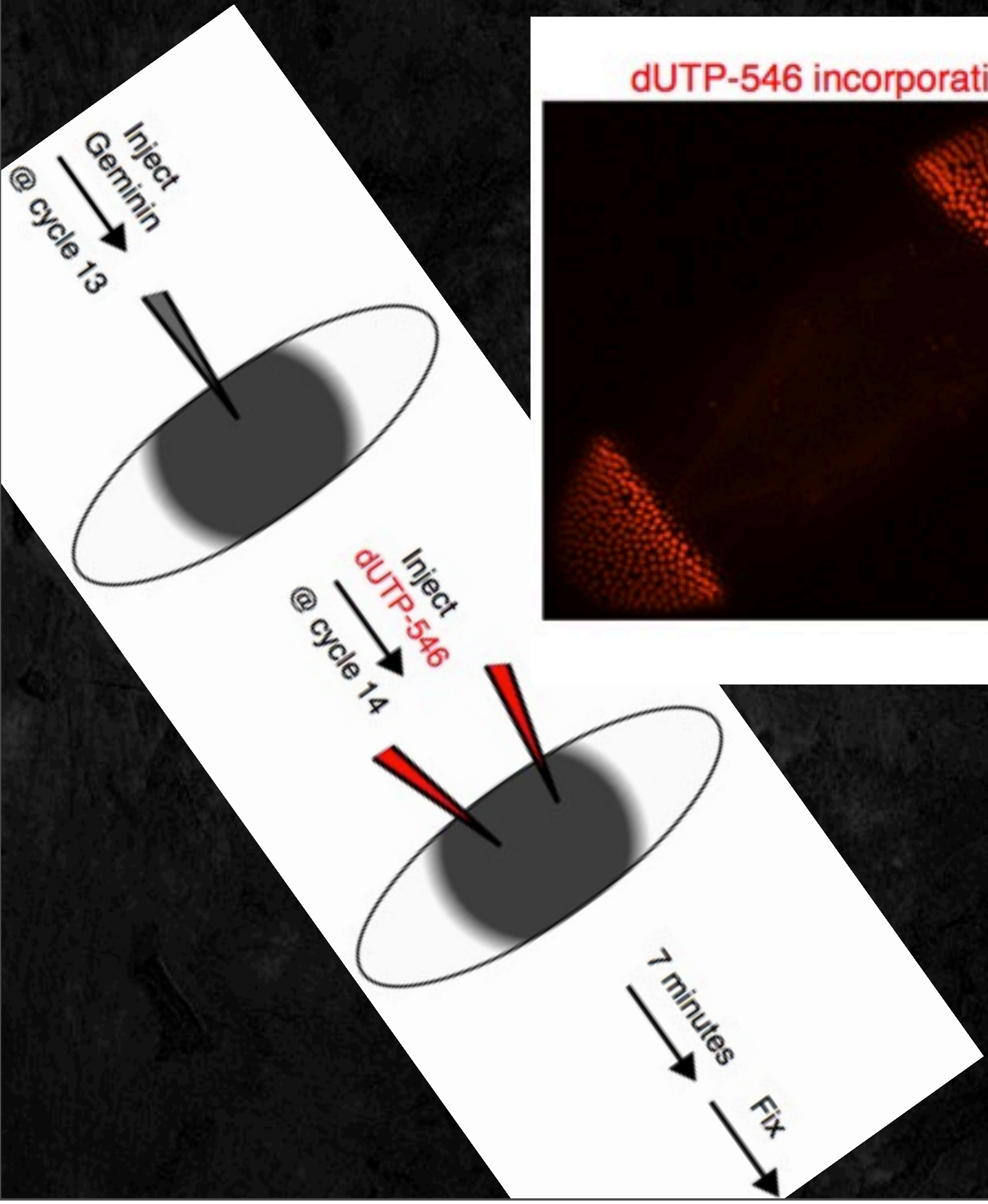
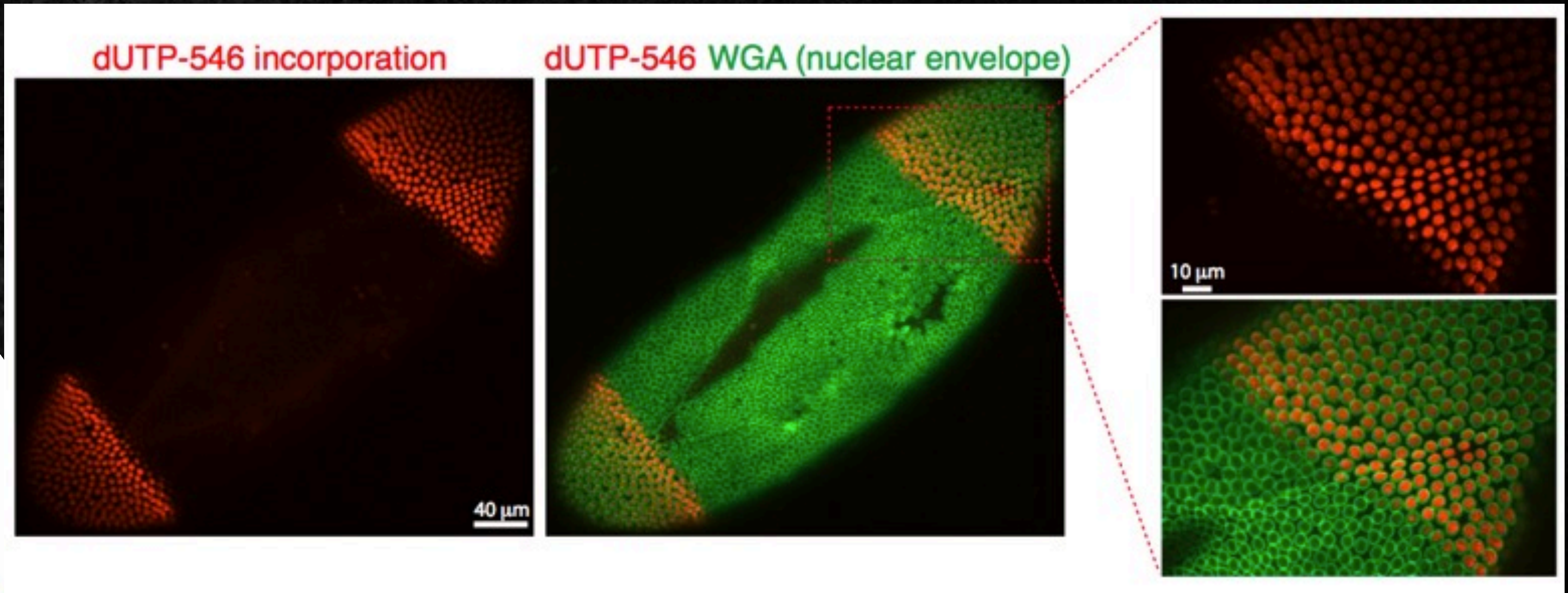


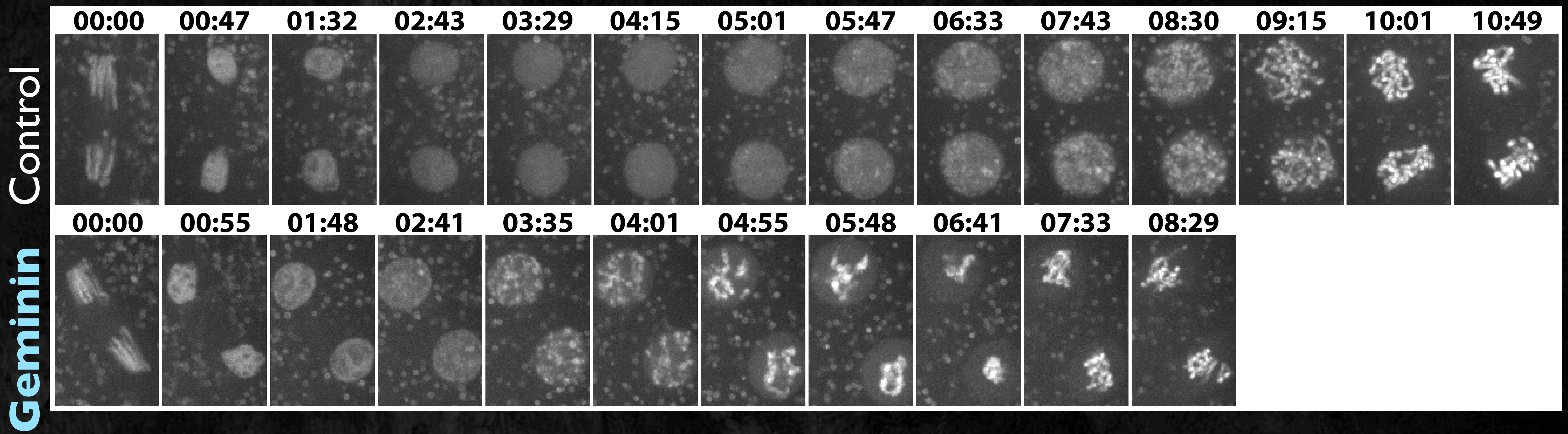




Deleting S phase Advances M in the early cycles

cycle 12

histone-GFP



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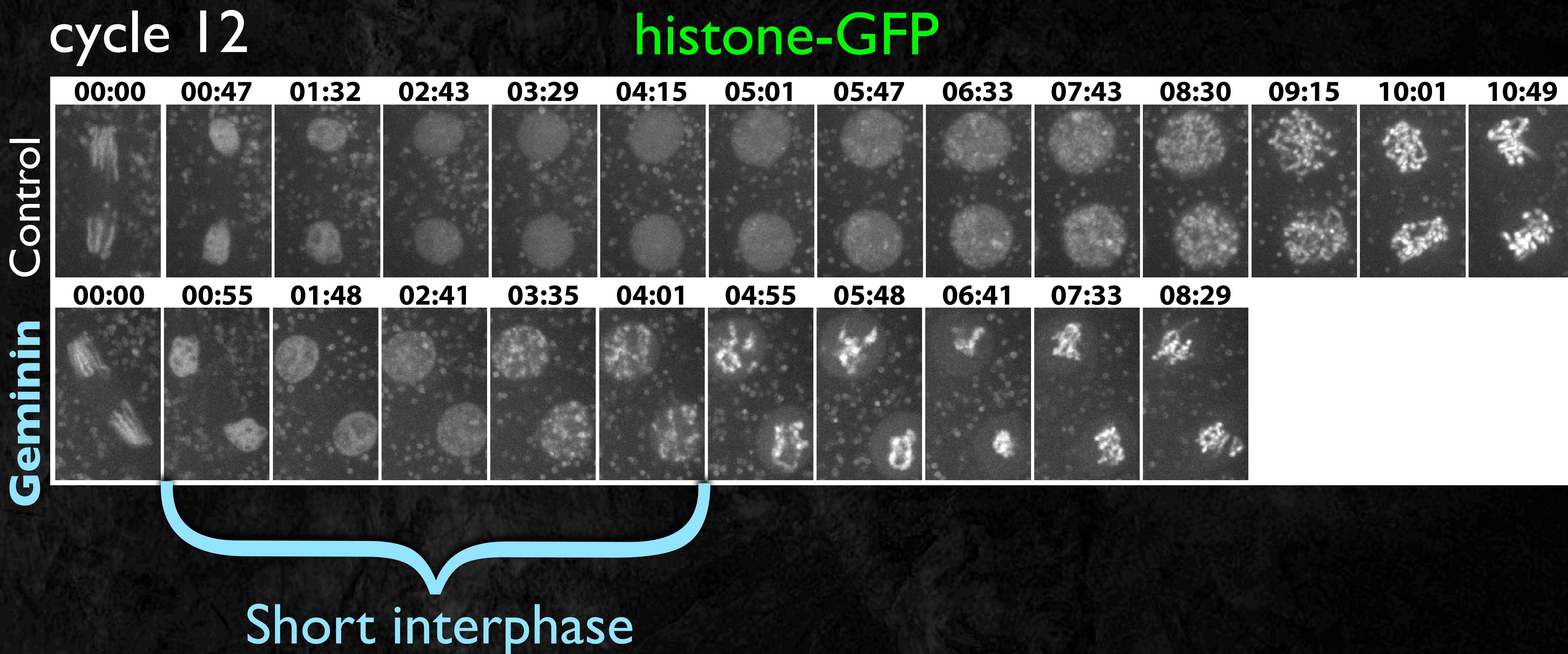

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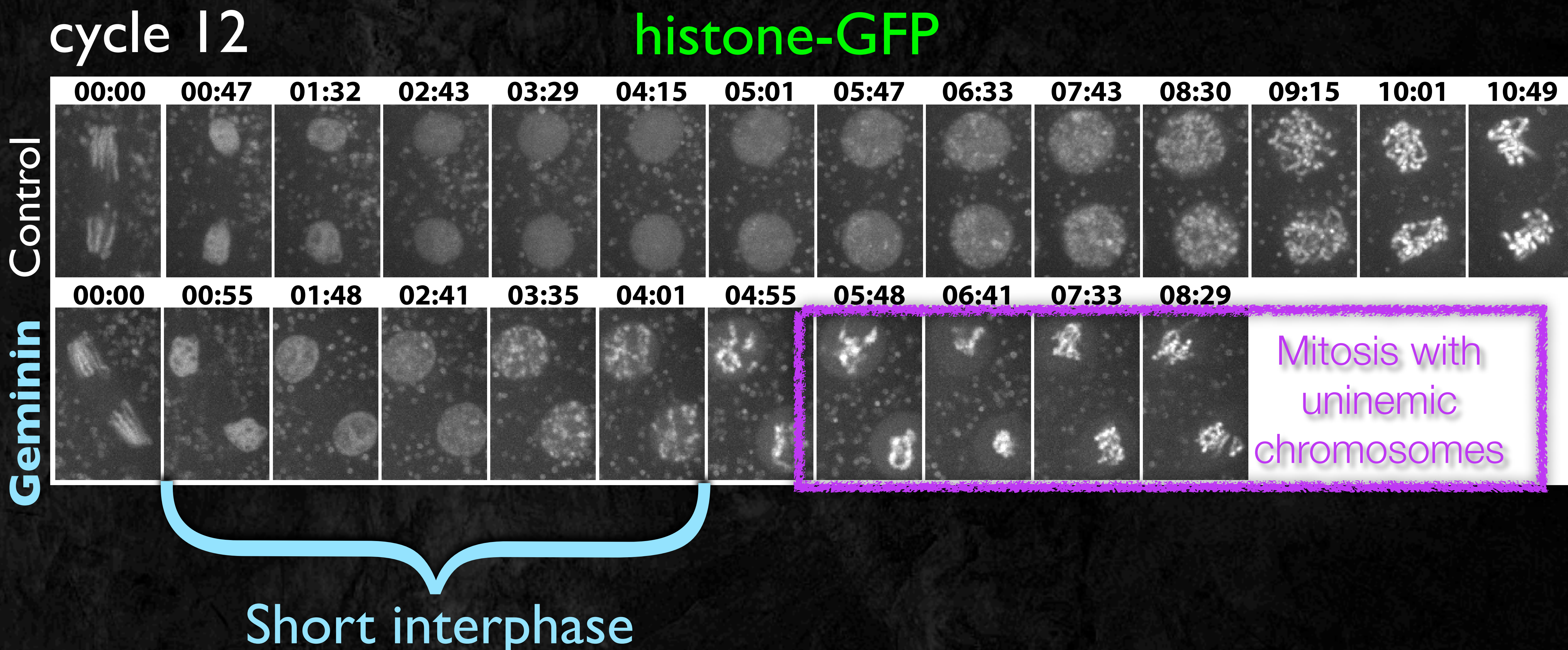
Deleting S phase Advances M in the early cycles



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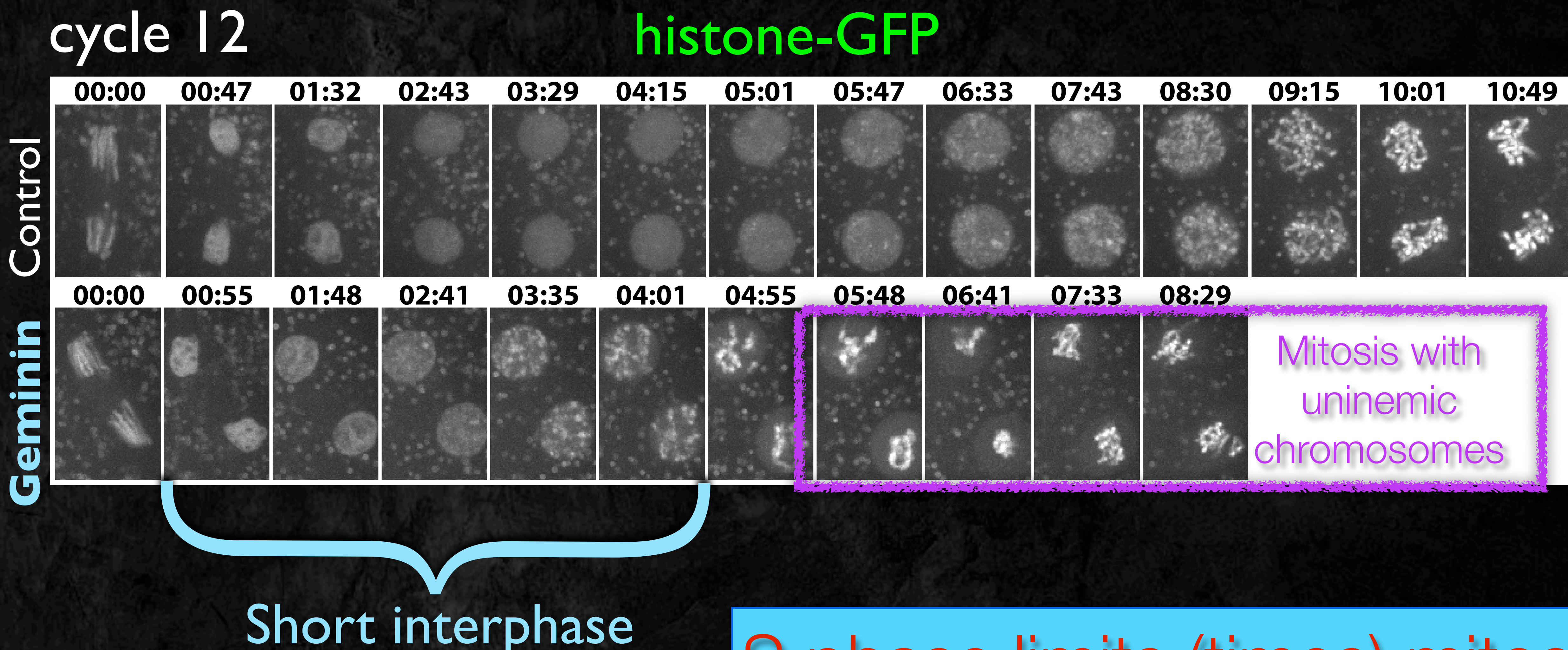
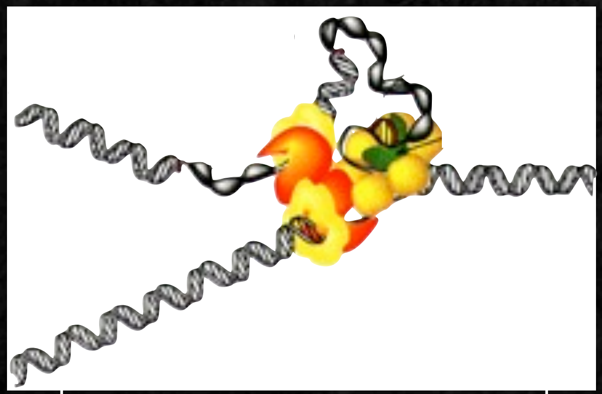


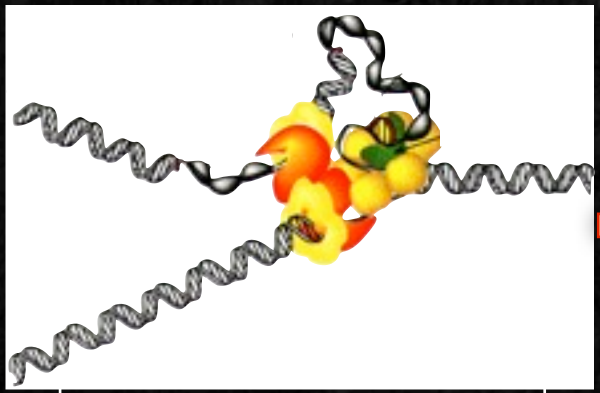
S phase limits (times) mitosis in pre-MBT cycles

How does a longer S phase delay Mitosis?



Replication

How does a longer S phase delay Mitosis?



Replication

induces →

Checkpoint kinase
Chk1/*grapes*

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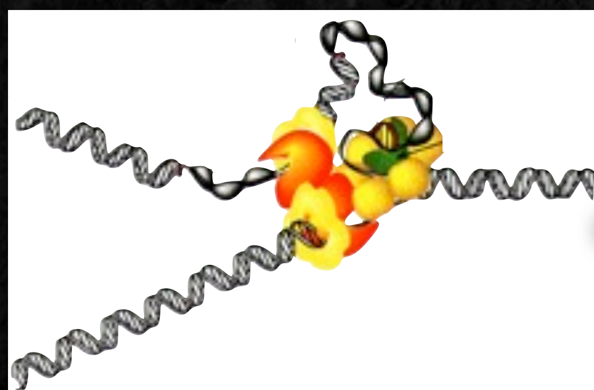

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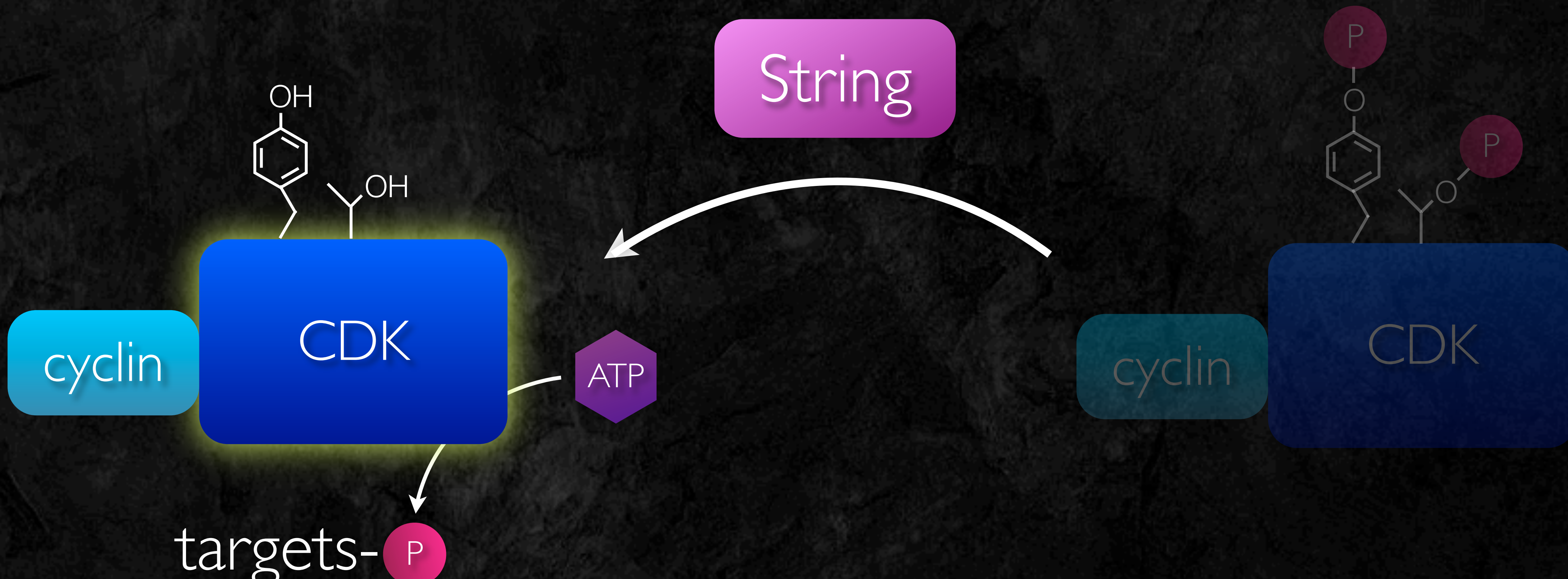

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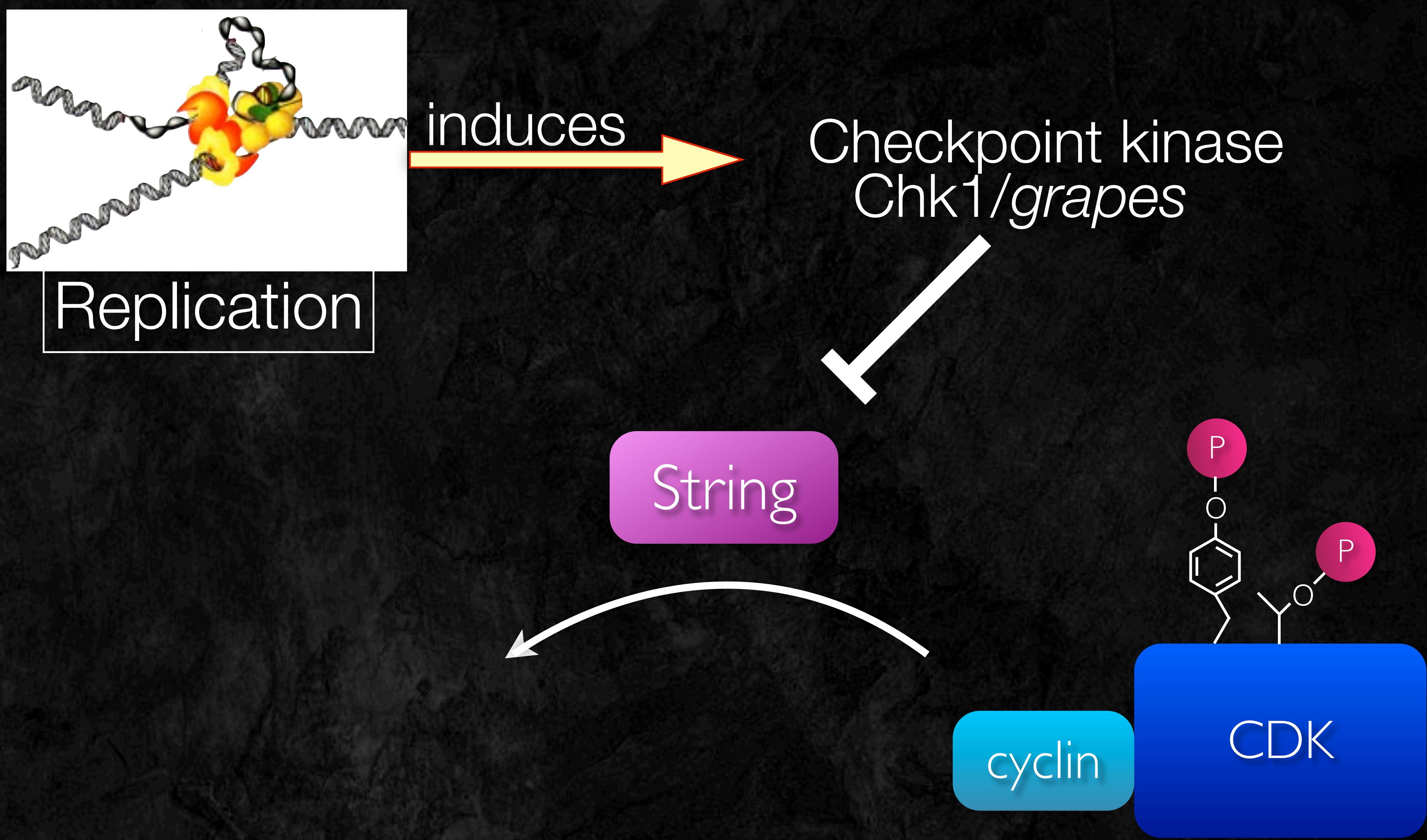


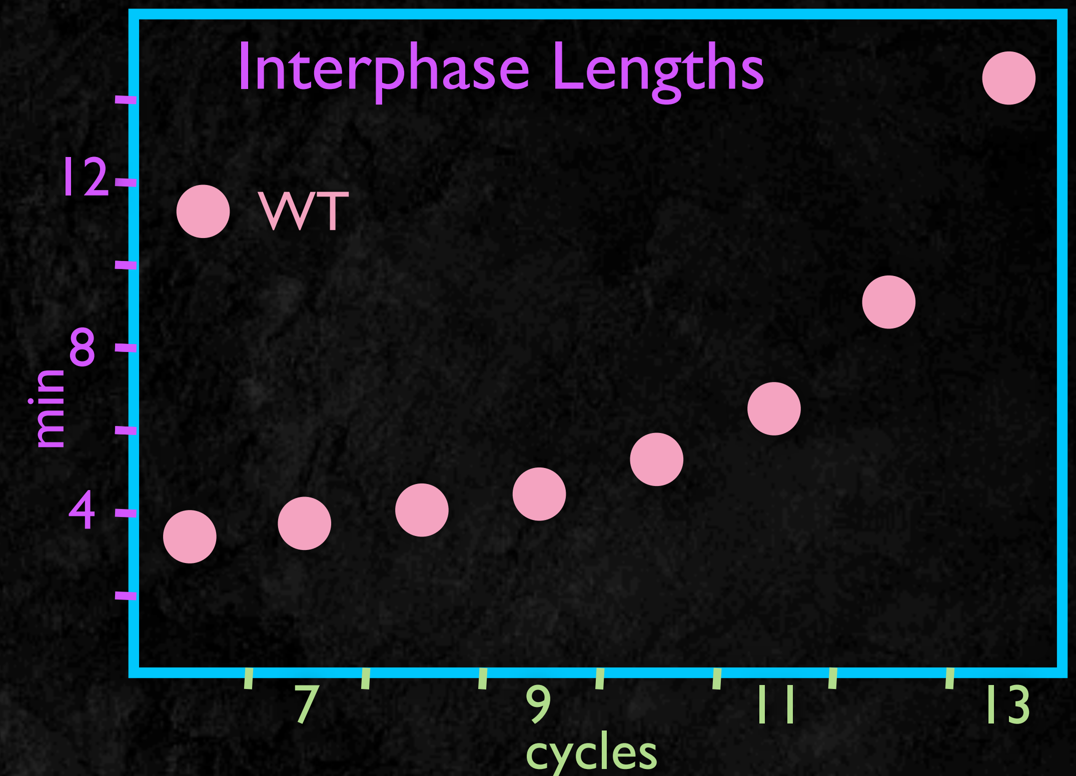
Check1*grapes* delays M pre MBT

Prior to MBT cycles get longer

Sibon, Stevenson & Theurkauf, 1997

Check1 *grapes* delays M pre MBT

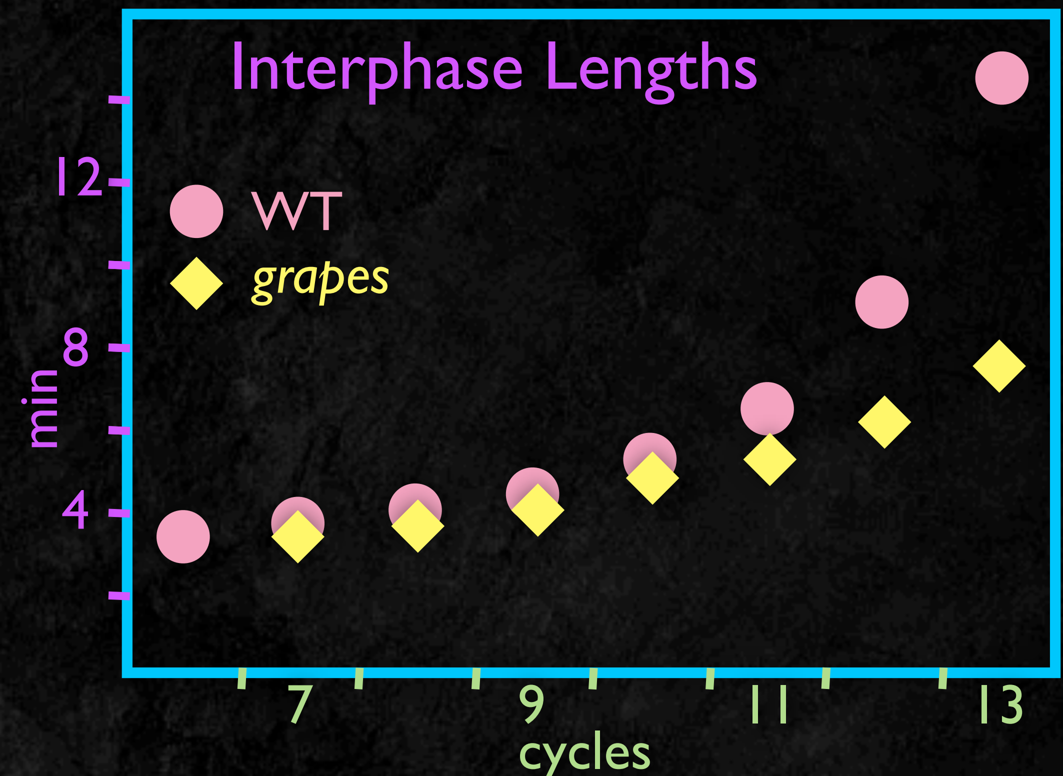
Prior to MBT cycles get longer



Sibon, Stevenson & Theurkauf, 1997

Check1 *grapes* delays M pre MBT

Prior to MBT cycles get longer

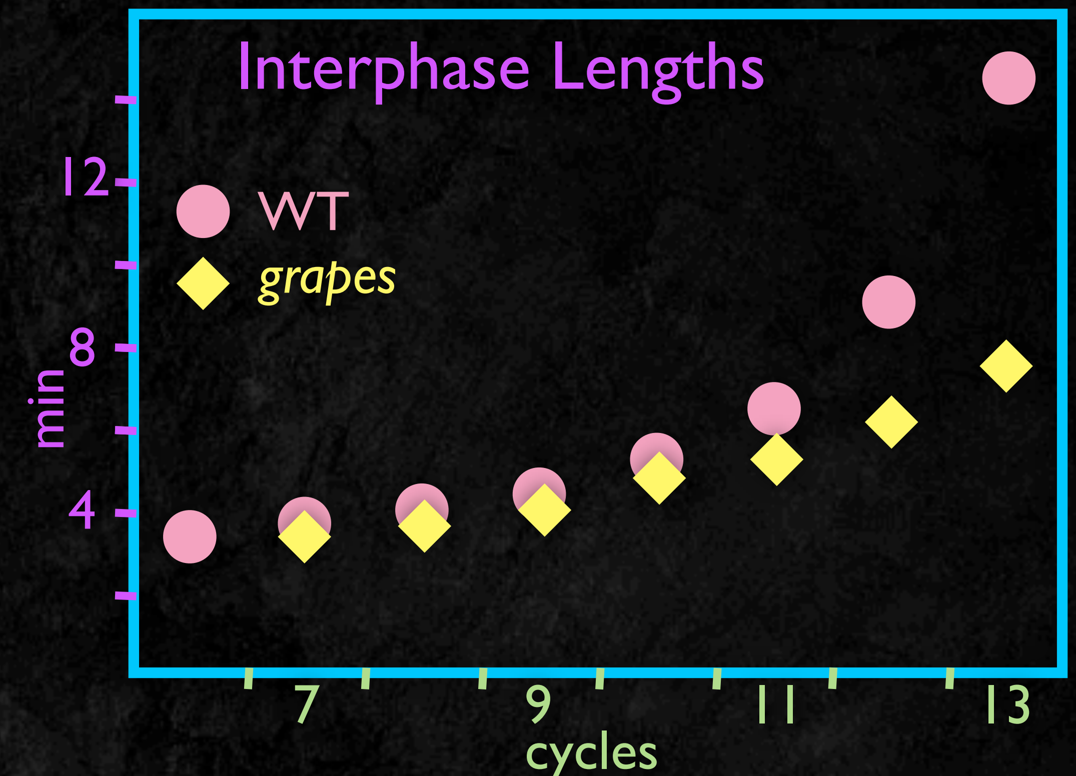


Sibon, Stevenson & Theurkauf, 1997

Check1*grapes* delays M pre MBT

Prior to MBT cycles get longer

Lengthening depends substantially on Grapes



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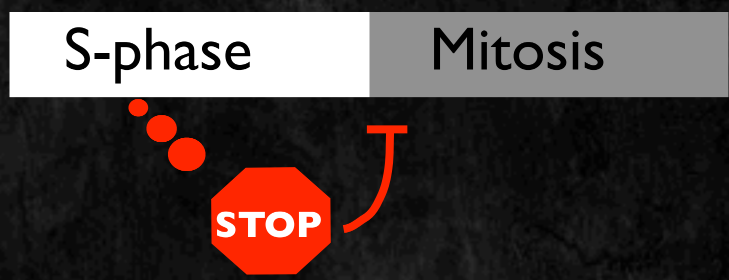

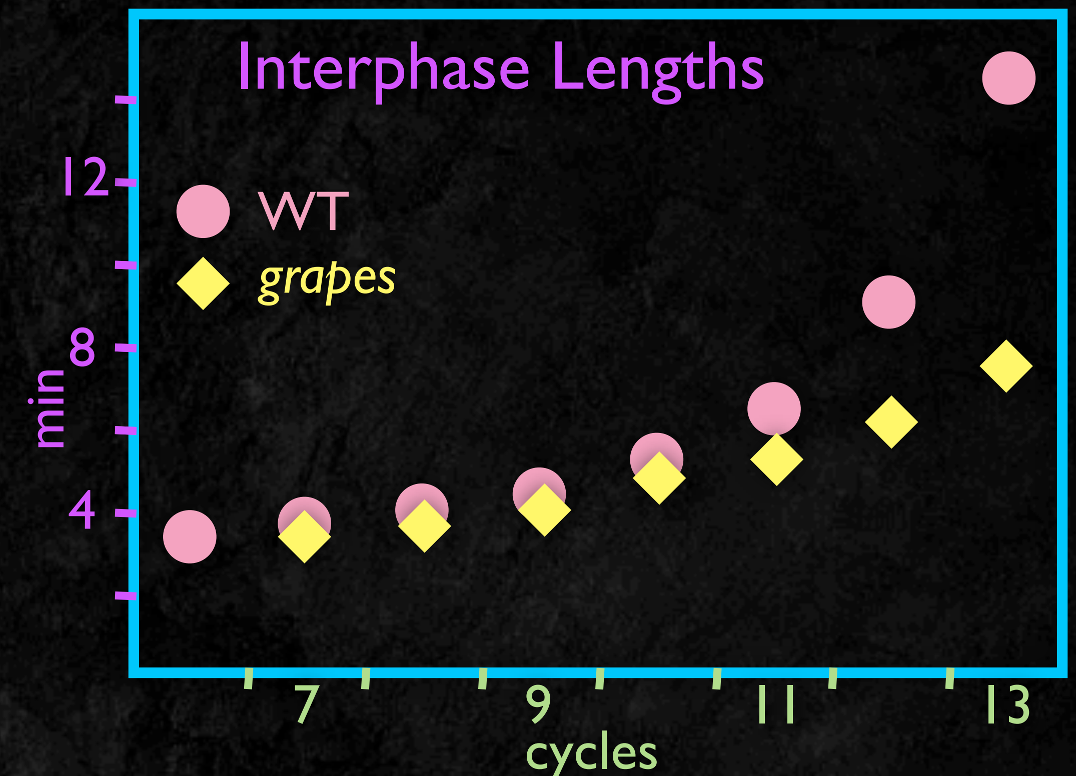

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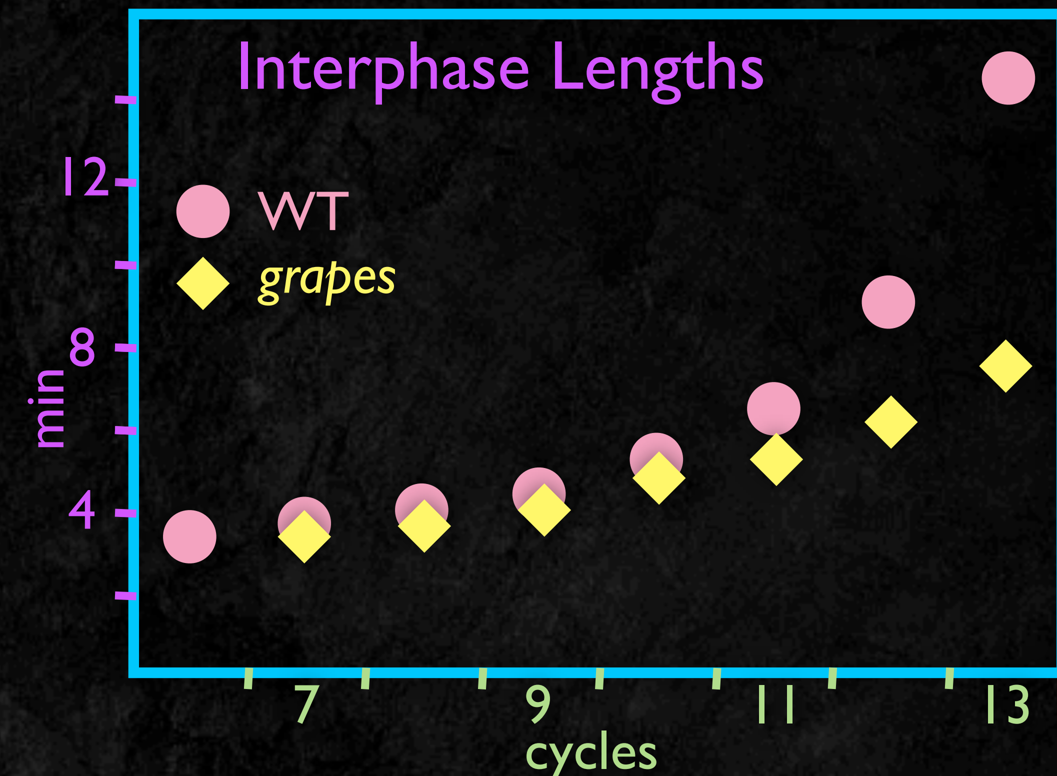
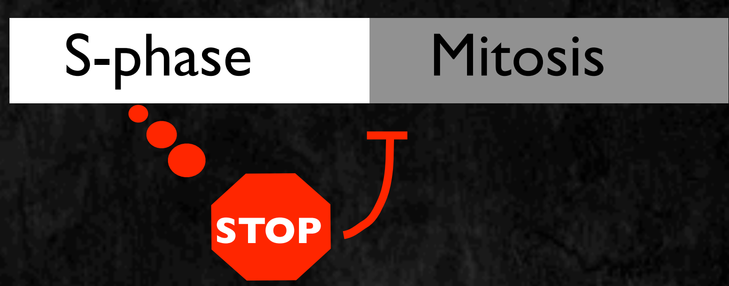


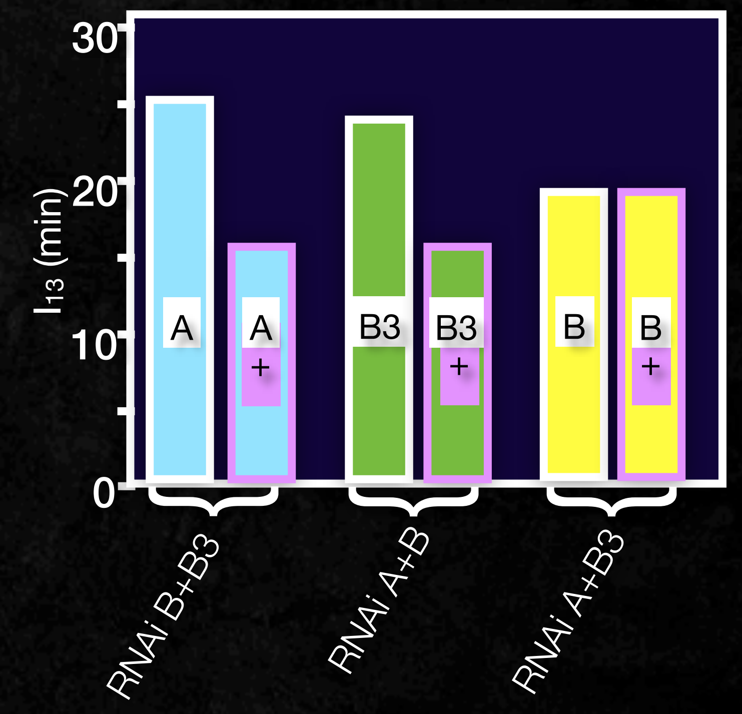
Lengthening depends substantially on Grapes



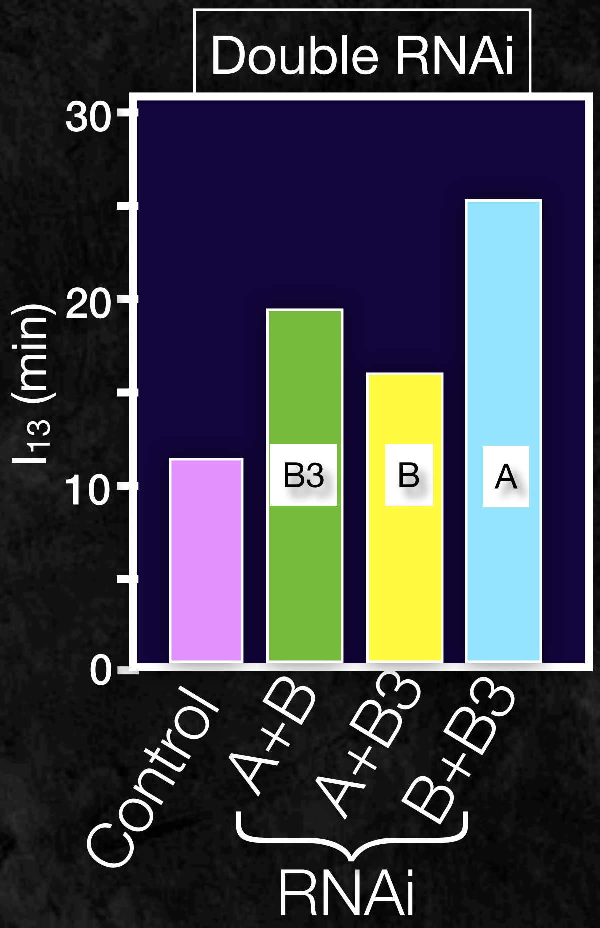
S phase → **Grapes** ⊣ **Mitosis** (nuclear density dependent?)

Sibon, Stevenson & Theurkauf, 1997

Return to cyclin type influence on interphase duration

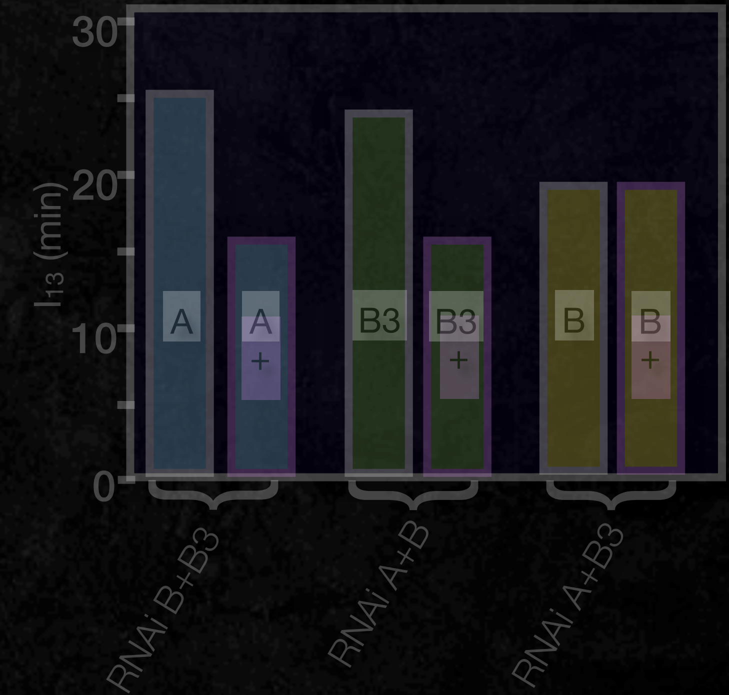


Return to cyclin type influence on interphase duration

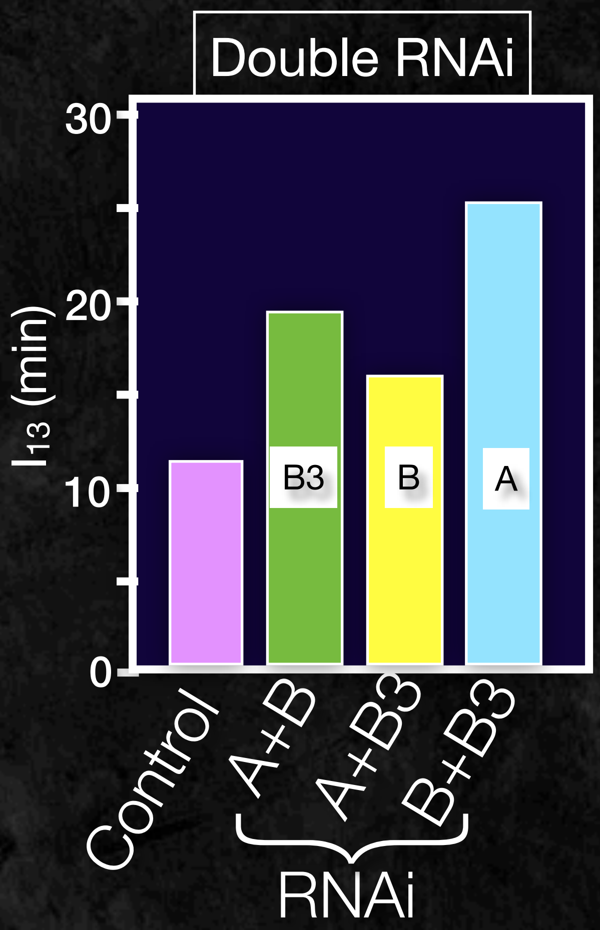


Interphase is longer

Is S longer?



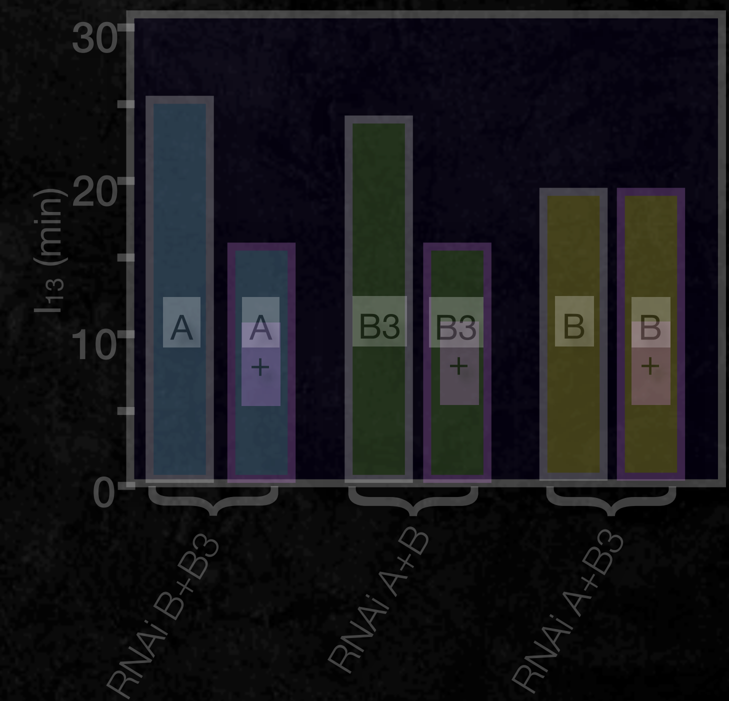
Return to cyclin type influence on interphase duration



Interphase is longer

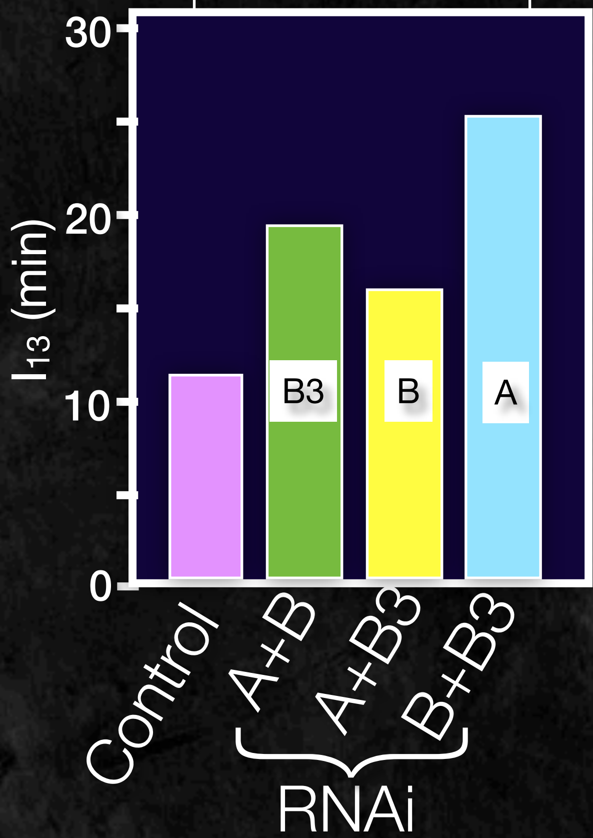
Is S longer?

Measure S phase



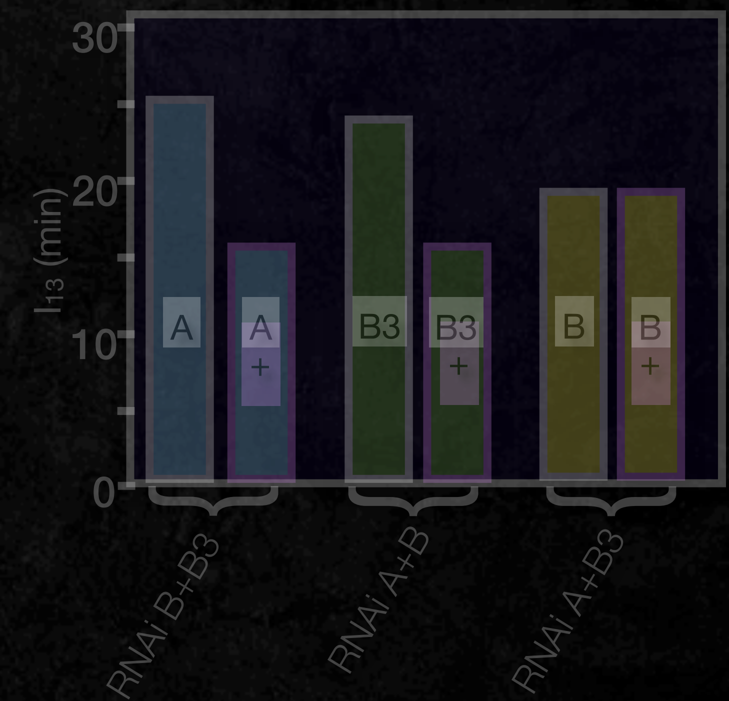
Return to cyclin type influence on interphase duration

Double RNAi



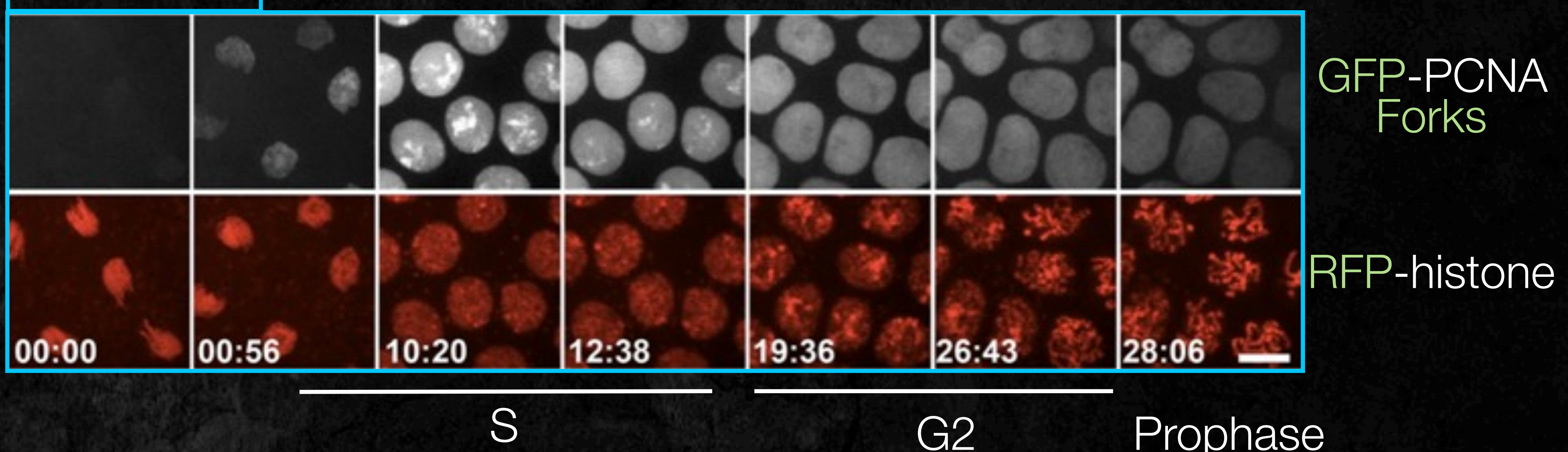
Interphase is longer

Is S longer?

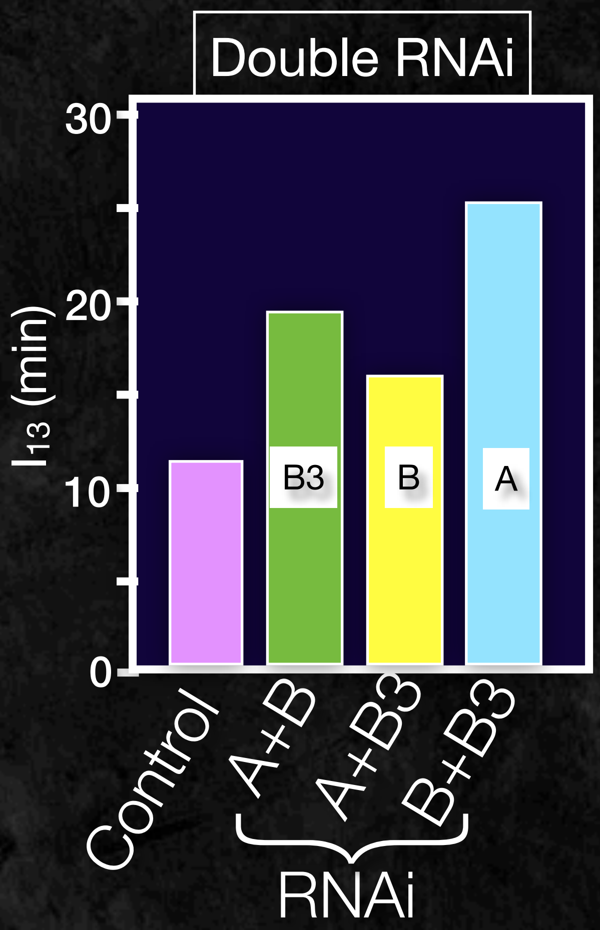


Measure S phase

RNAi B+B3



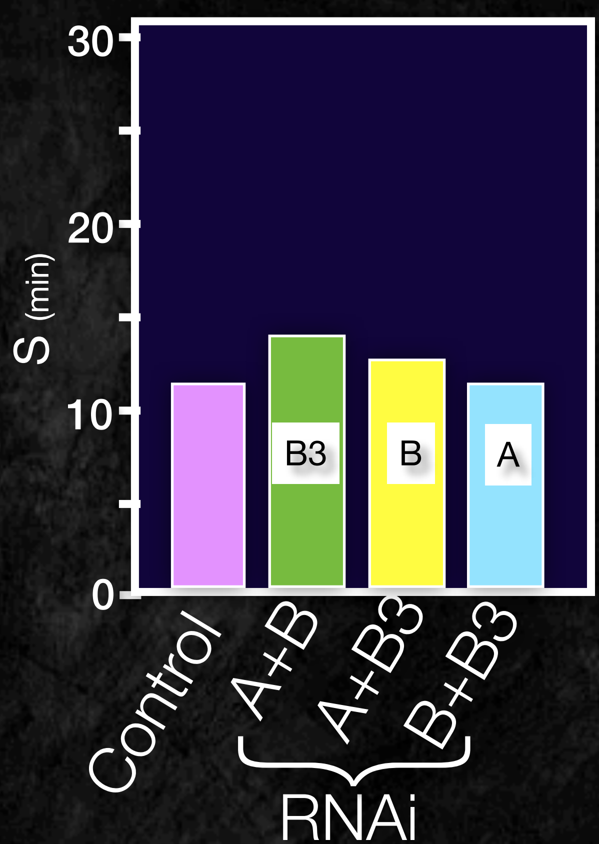
Return to cyclin type influence on interphase duration



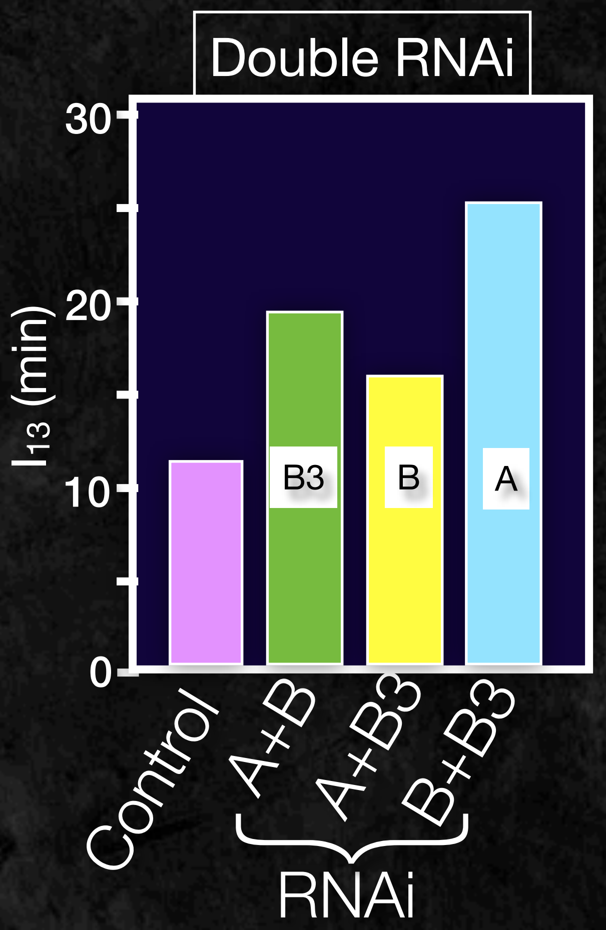
Interphase is longer

Is S longer?

Measure S phase



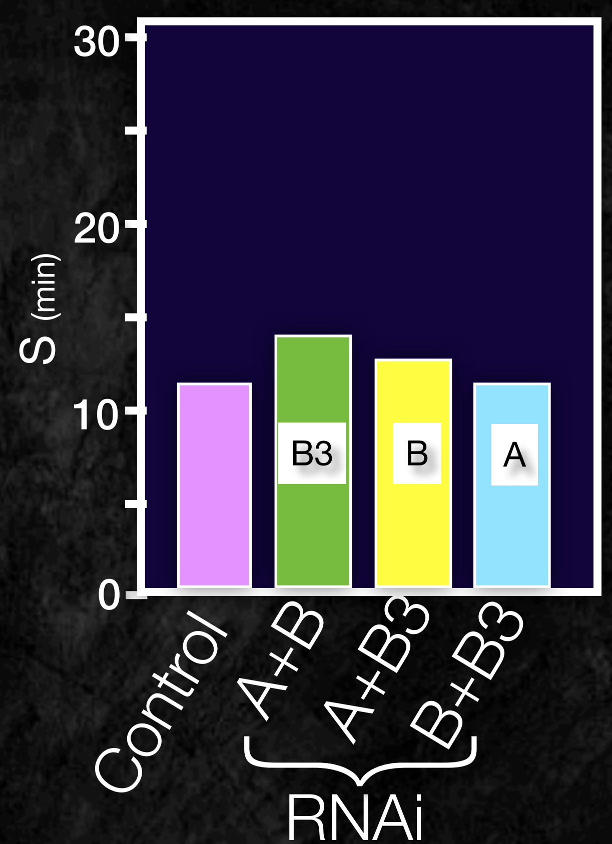
Return to cyclin type influence on interphase duration

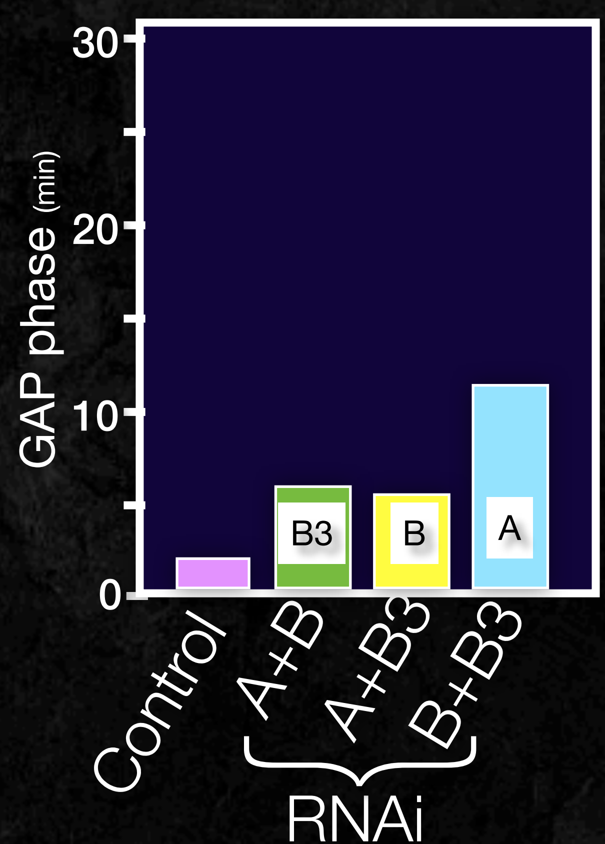


Interphase is longer

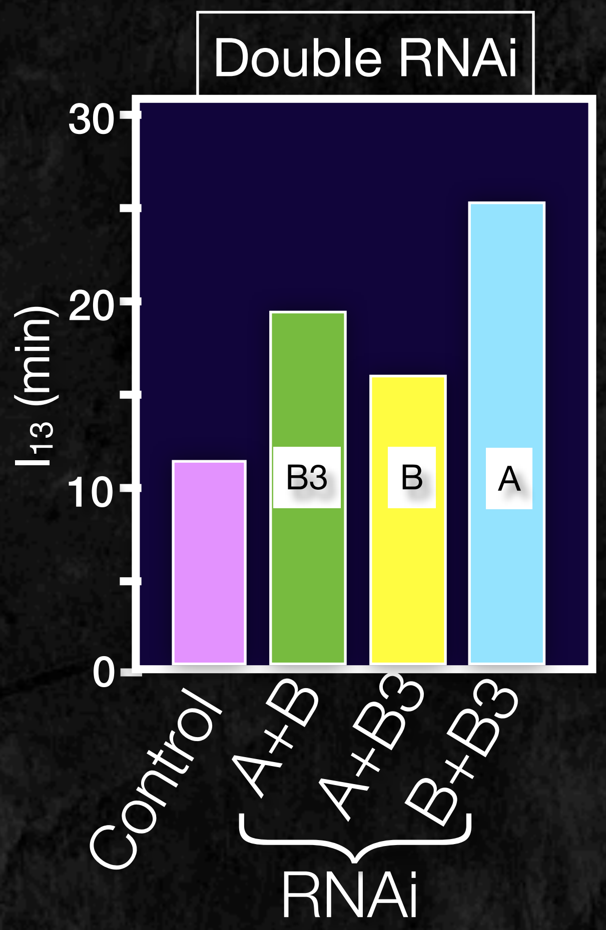
Is S longer?

Measure S phase

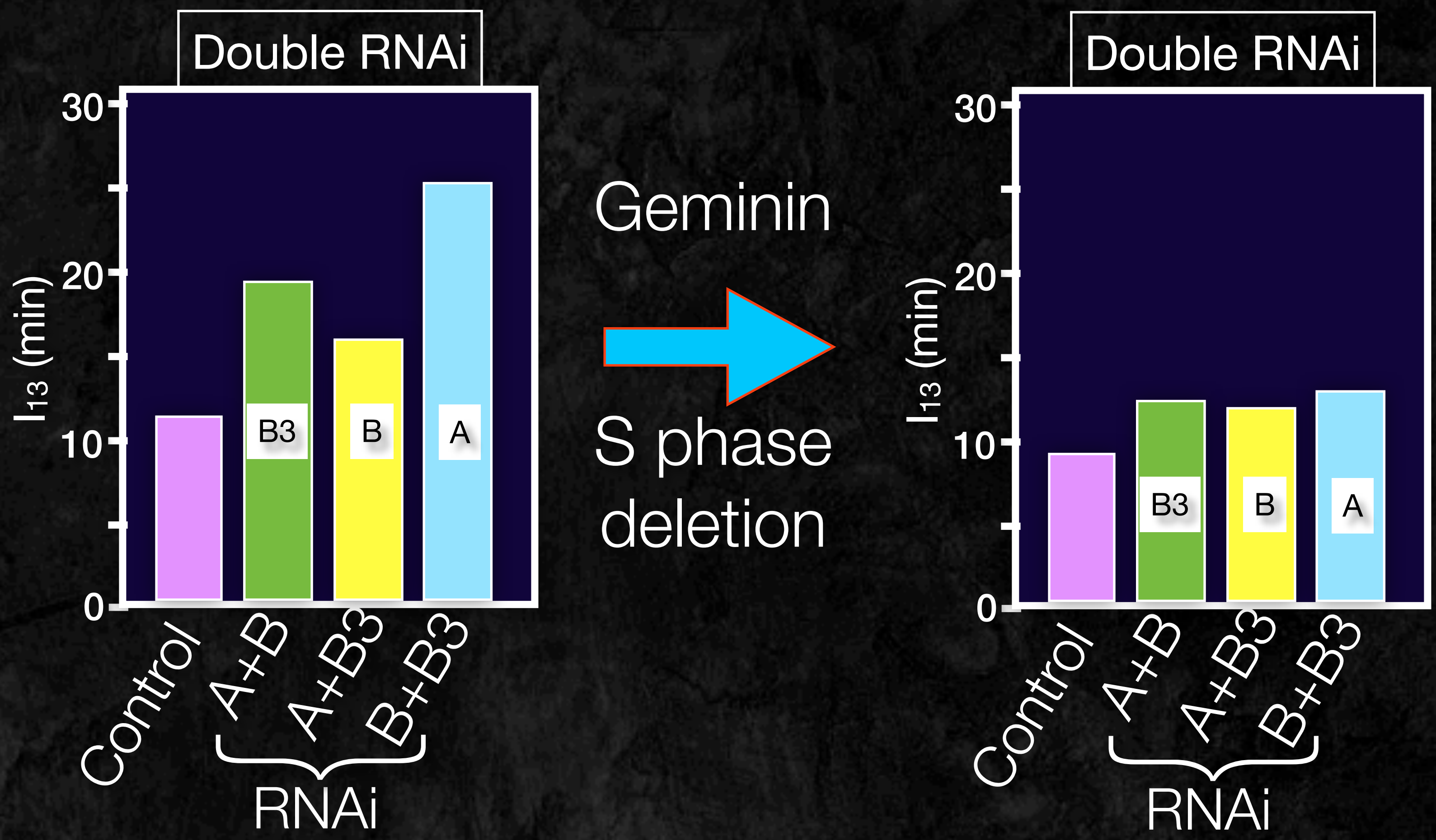




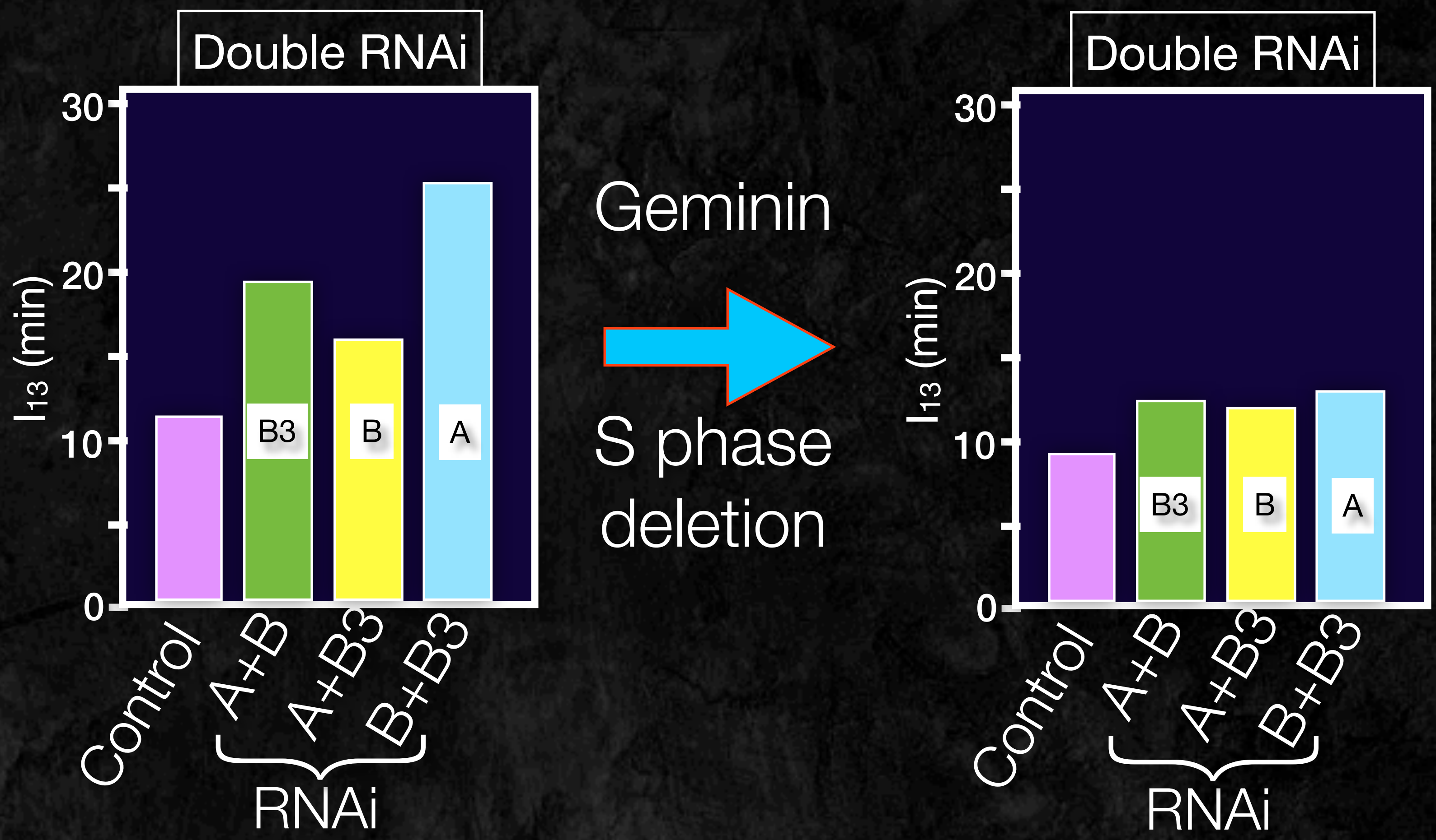
Does prolongation of interphase depend on S?



Does prolongation of interphase depend on S?

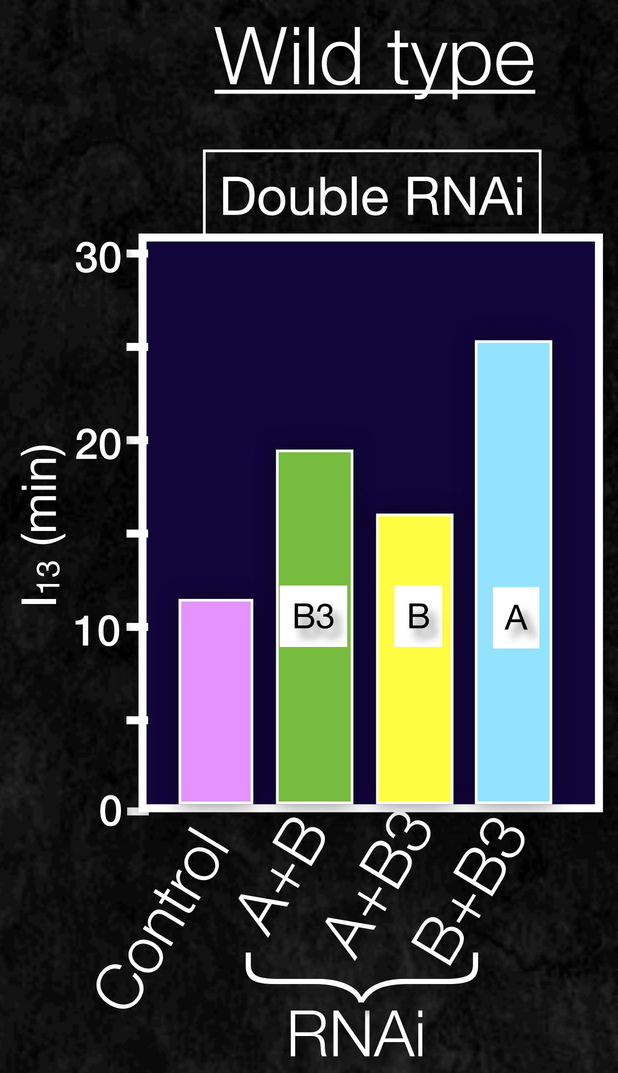


Does prolongation of interphase depend on S?



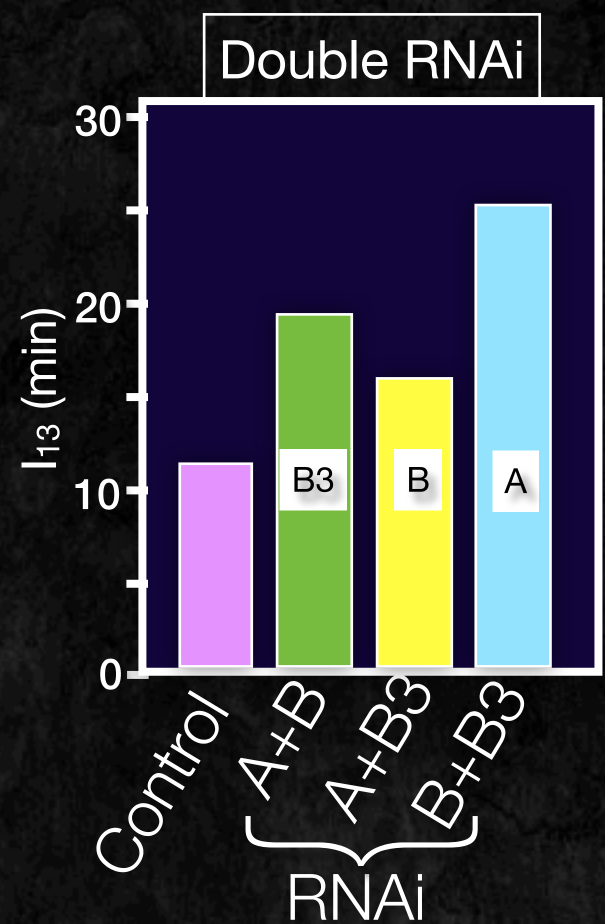
<u>YES</u>
G2 gone
and
interphase shorter

The G2 also depends on the checkpoint



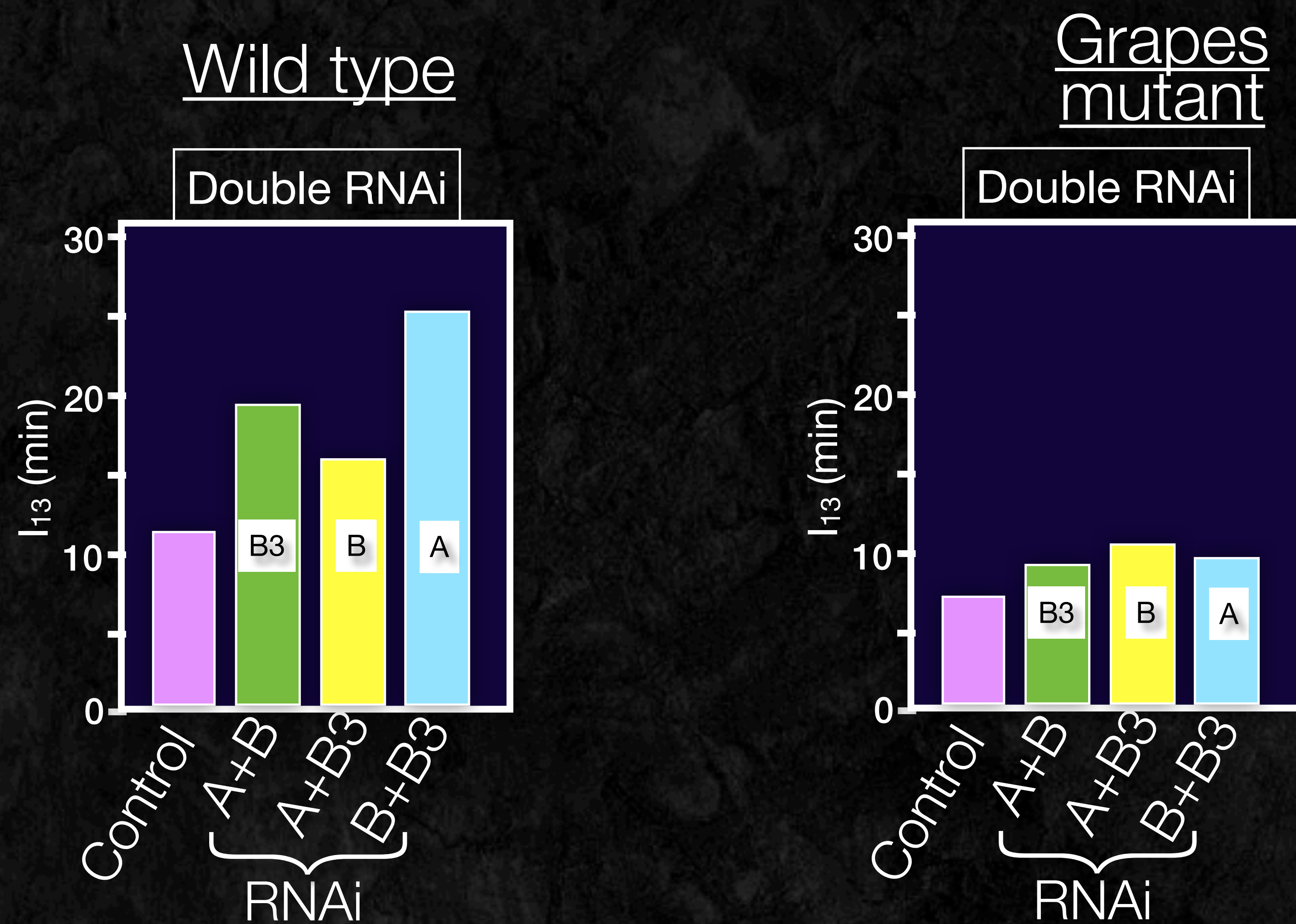
The G2 also depends on the checkpoint

Wild type

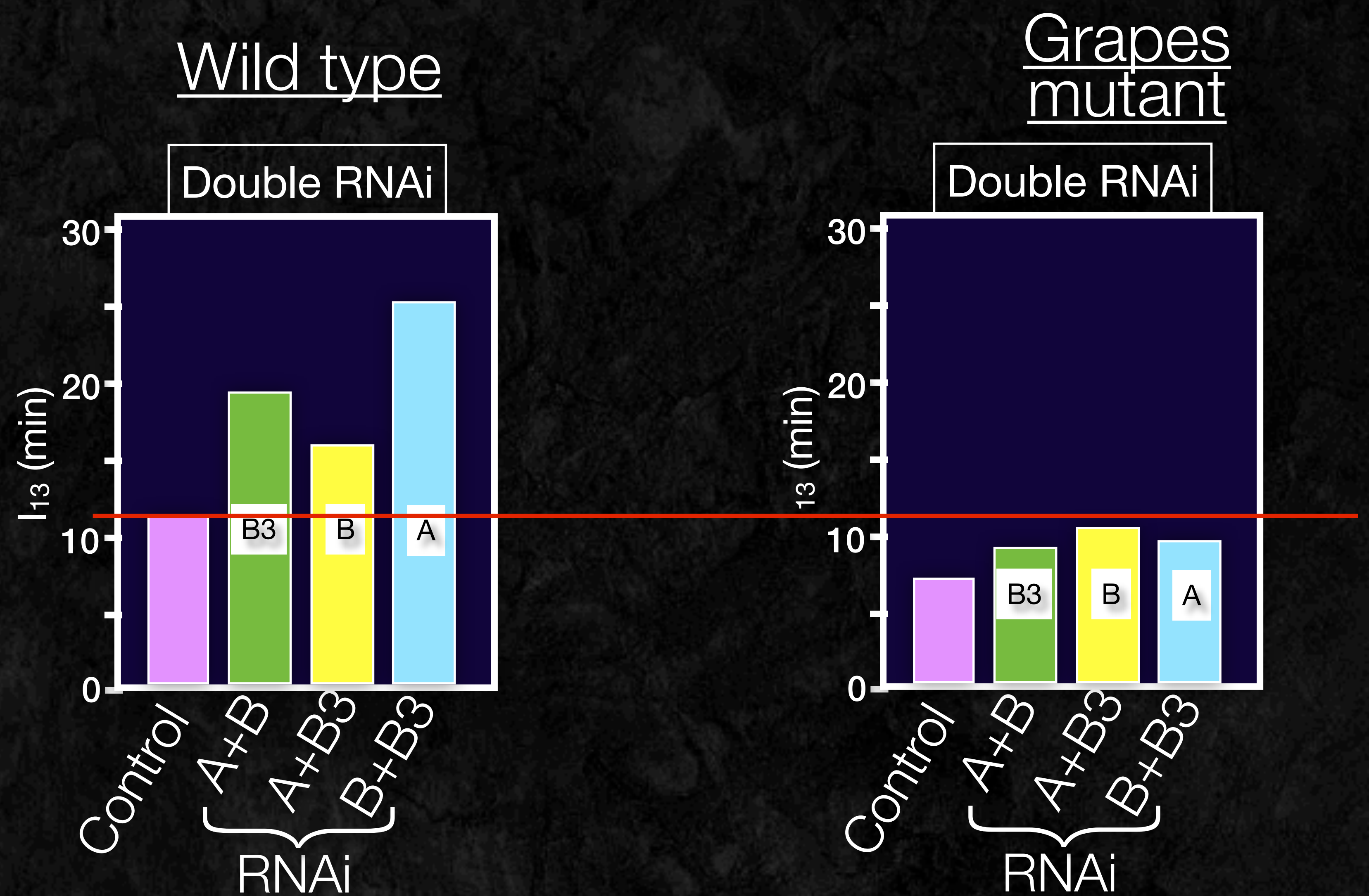


Grapes mutant

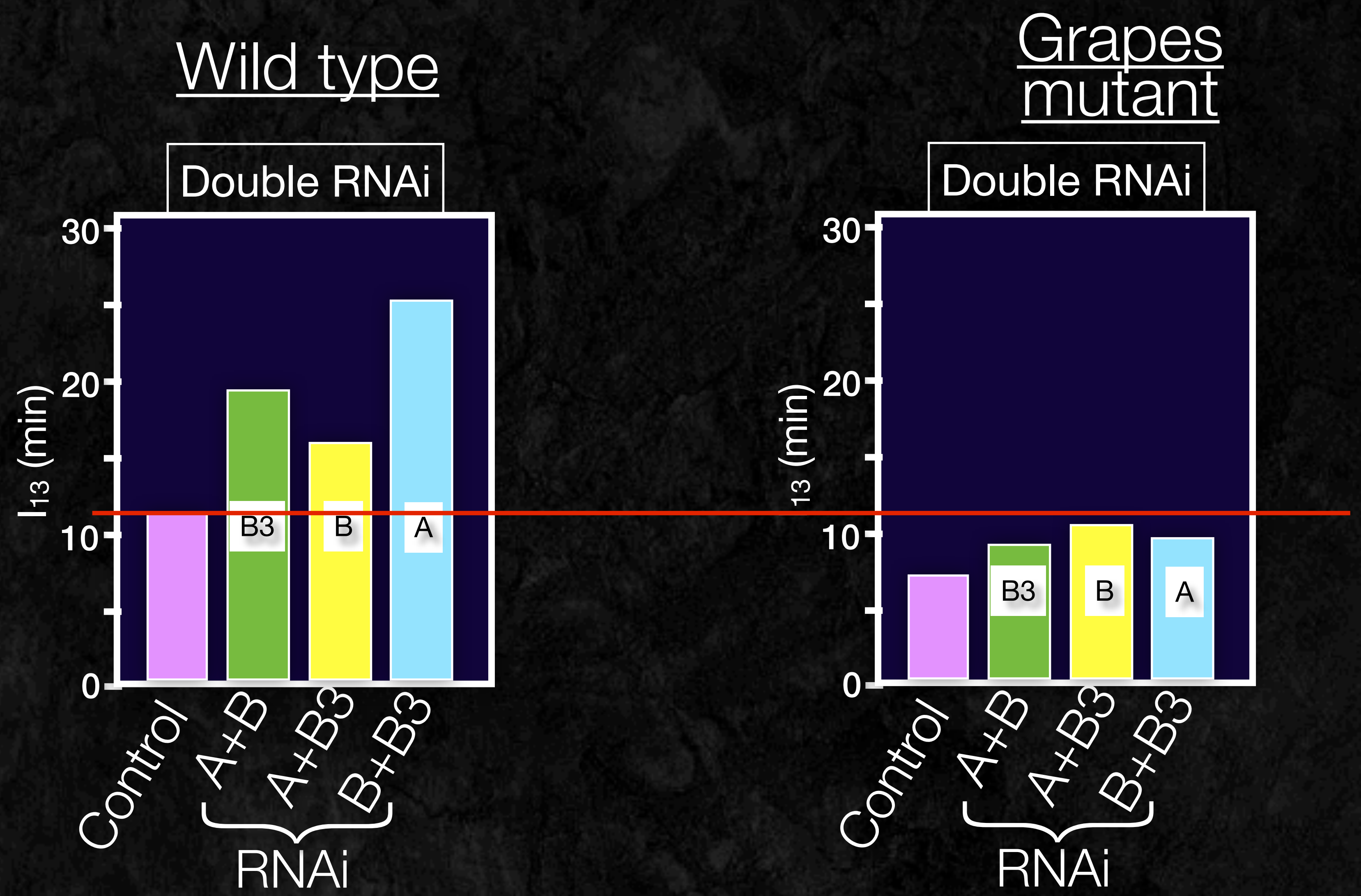
The G2 also depends on the checkpoint



The G2 also depends on the checkpoint

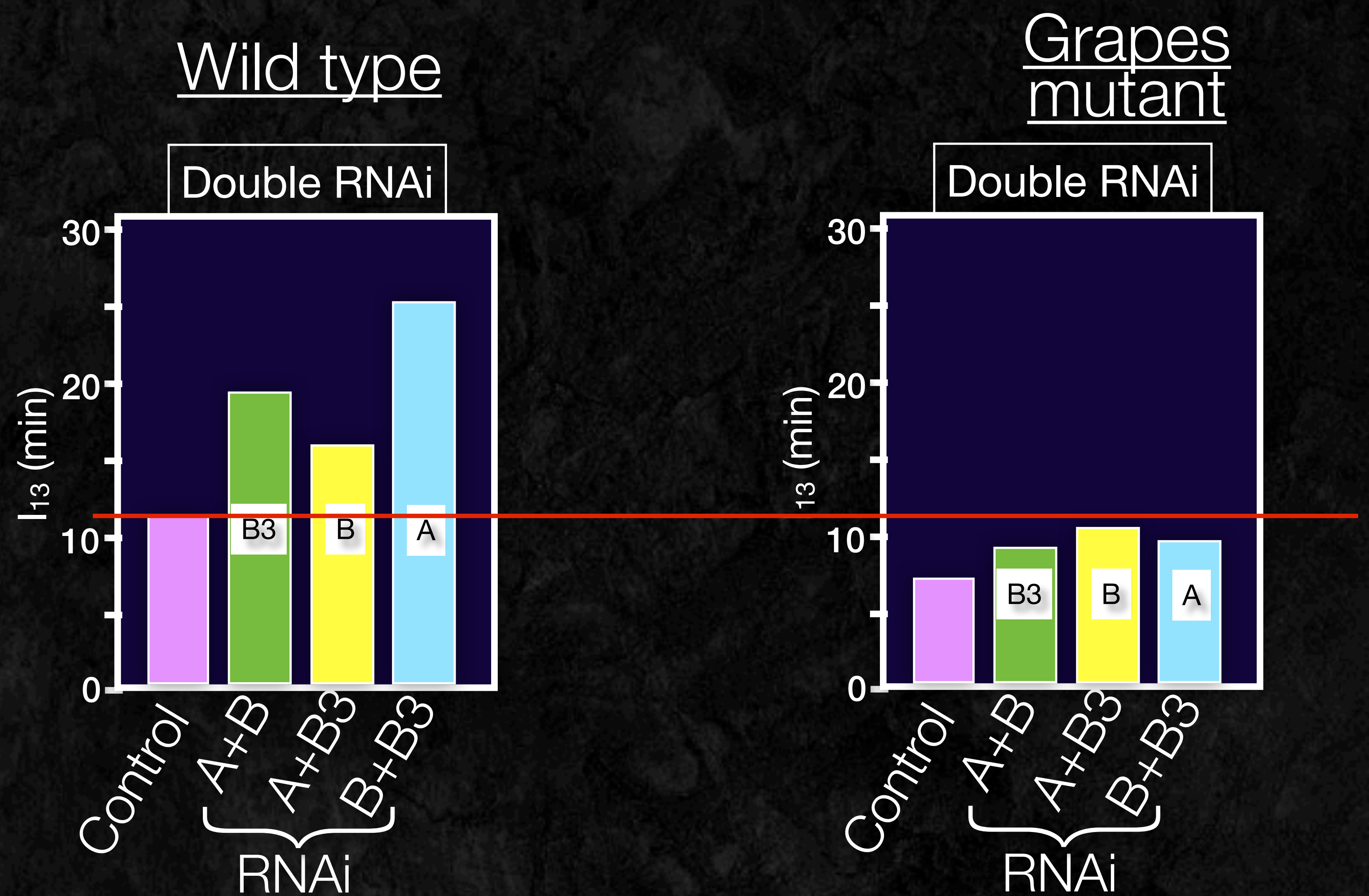


The G2 also depends on the checkpoint



In the absence of grapes each single cyclin drives early mitosis & most of the difference in interphase length disappears

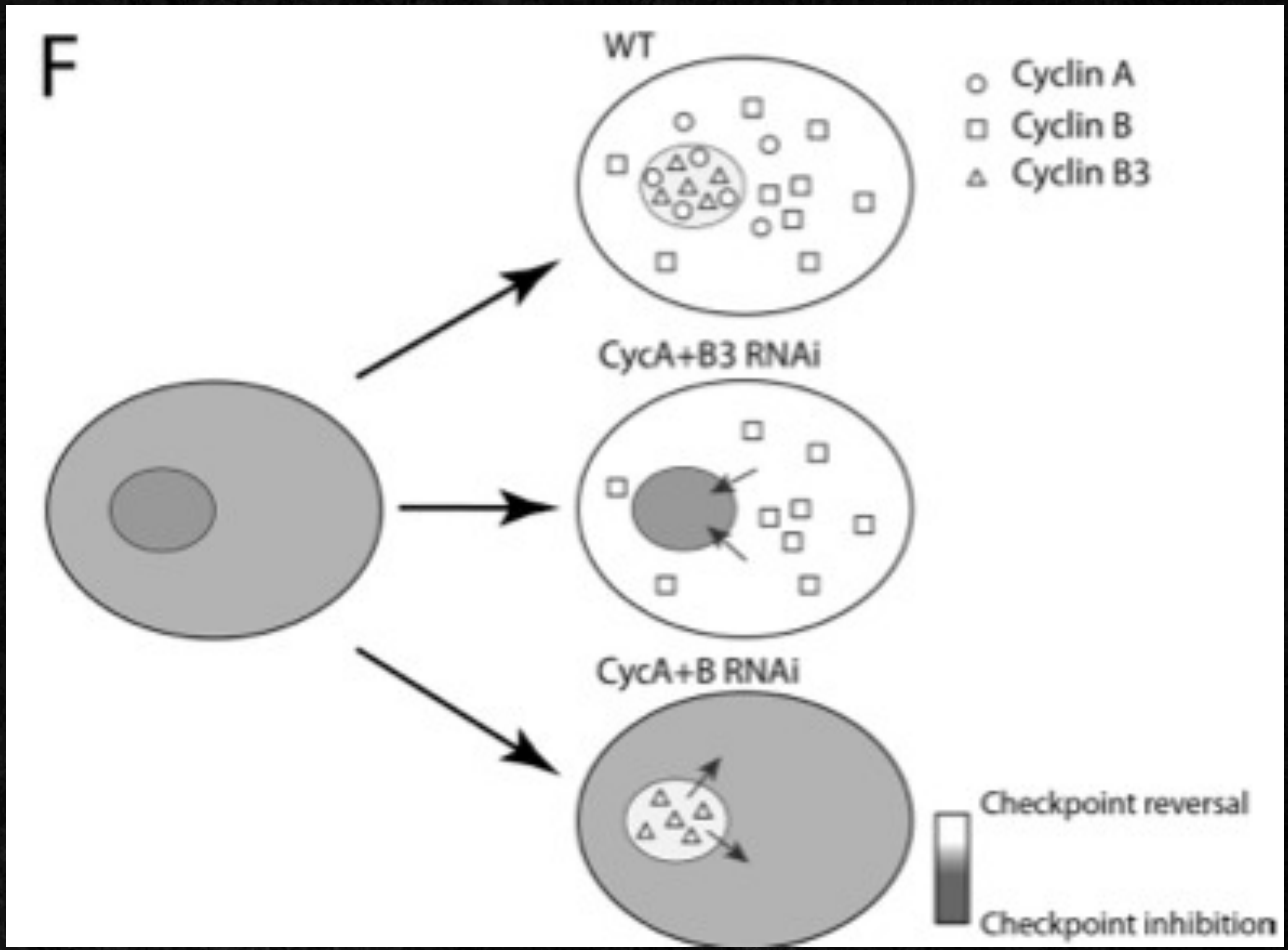
The G2 also depends on the checkpoint



In the absence of grapes each single cyclin drives early mitosis & most of the difference in interphase length disappears

Conclude multiple cyclin types collaborate to reverse the checkpoint

Model: Compartment specific reversal of the checkpoint



S phase length dictates interphase duration pre-MBT

S phase length dictates interphase duration pre-MBT

How does S phase get long?

S phase length dictates interphase duration pre-MBT

Tony Shermoen

How does S phase get long?

S phase Duration

S2-S7 ~ 3.4 min

S14~ 55 min

S phase in disc - ~ 8hr (480 min)

S phase Duration

S2-S7 ~ 3.4 min

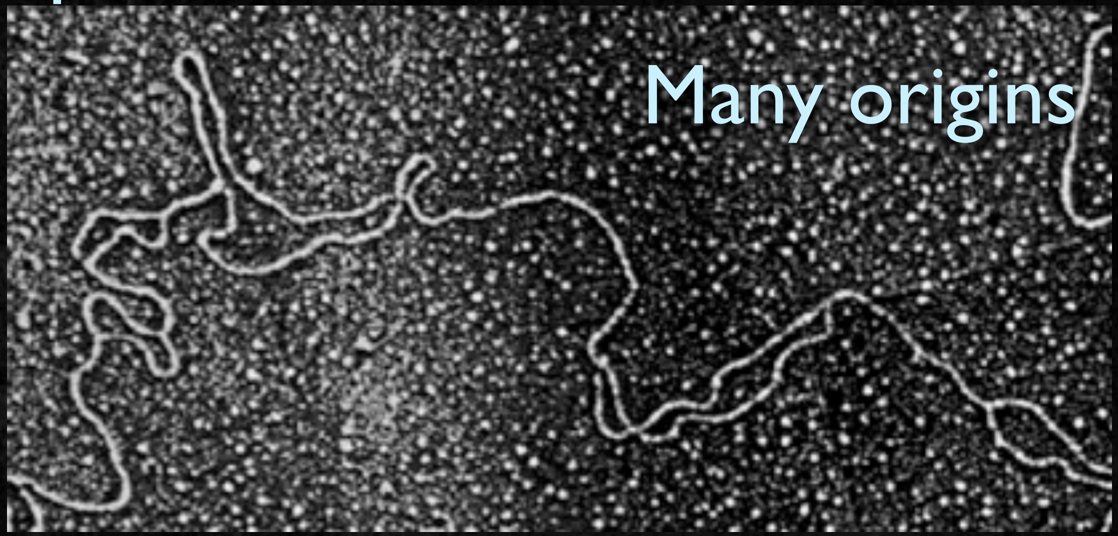
S14~ 55 min >100x

S phase in disc - ~ 8hr (480 min)

S phase Duration

For Speed

S2-S7 ~ 3.4 min



S14~ 55 min

>100x

S phase in disc - ~ 8hr (480 min)

S phase Duration

S2-S7 ~ 3.4 min

For Speed

- Frequent origins: ave. every 8 kb
- All origins fire at the same time

S14~ 55 min

>100x

S phase in disc - ~ 8hr (480 min)

S phase Duration

S2-S7 ~ 3.4 min

For Speed

Frequent origins: ave. every 8 kb

All origins fire at the same time

S14~ 55 min

>100x

S phase in disc - ~ 8hr (480 min)

For relaxed pace

Origins spaced ~ 40 kb

Not all origins fire at the same time

Prolongation of S linked to heterochromatin formation

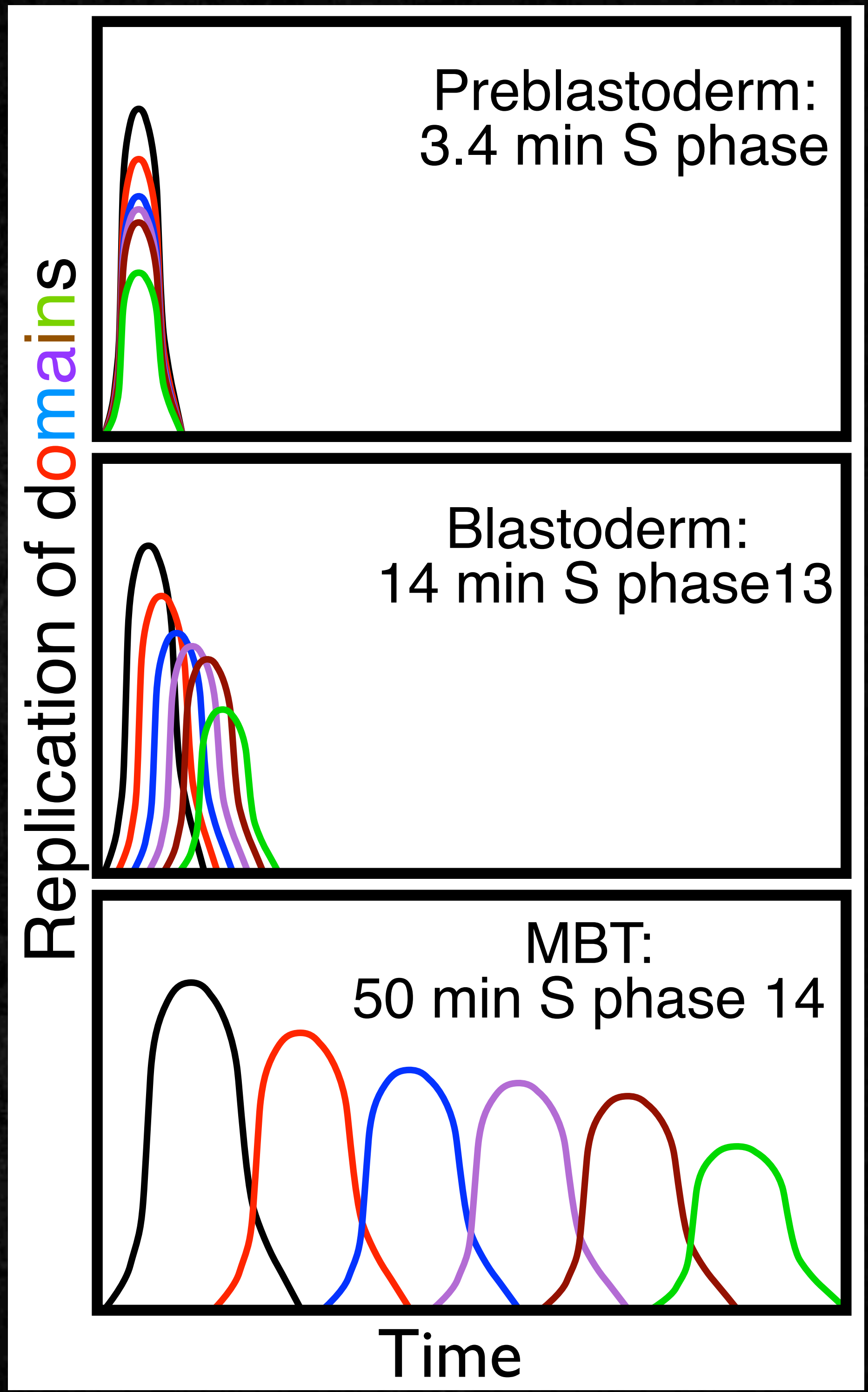
Uniform rapid replication

Early developmental program

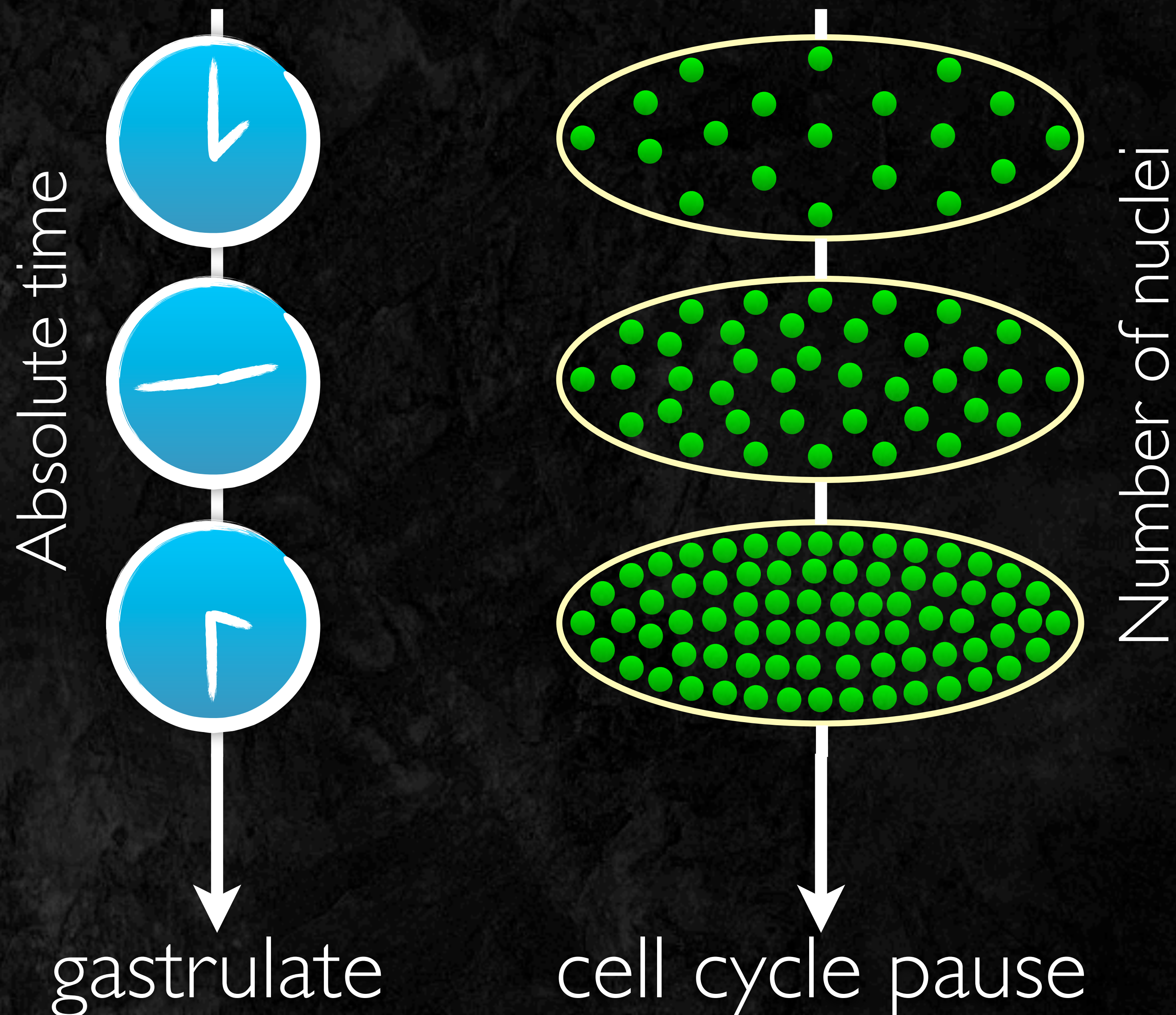
Satellite sequences

"Constitutive" heterochromatin

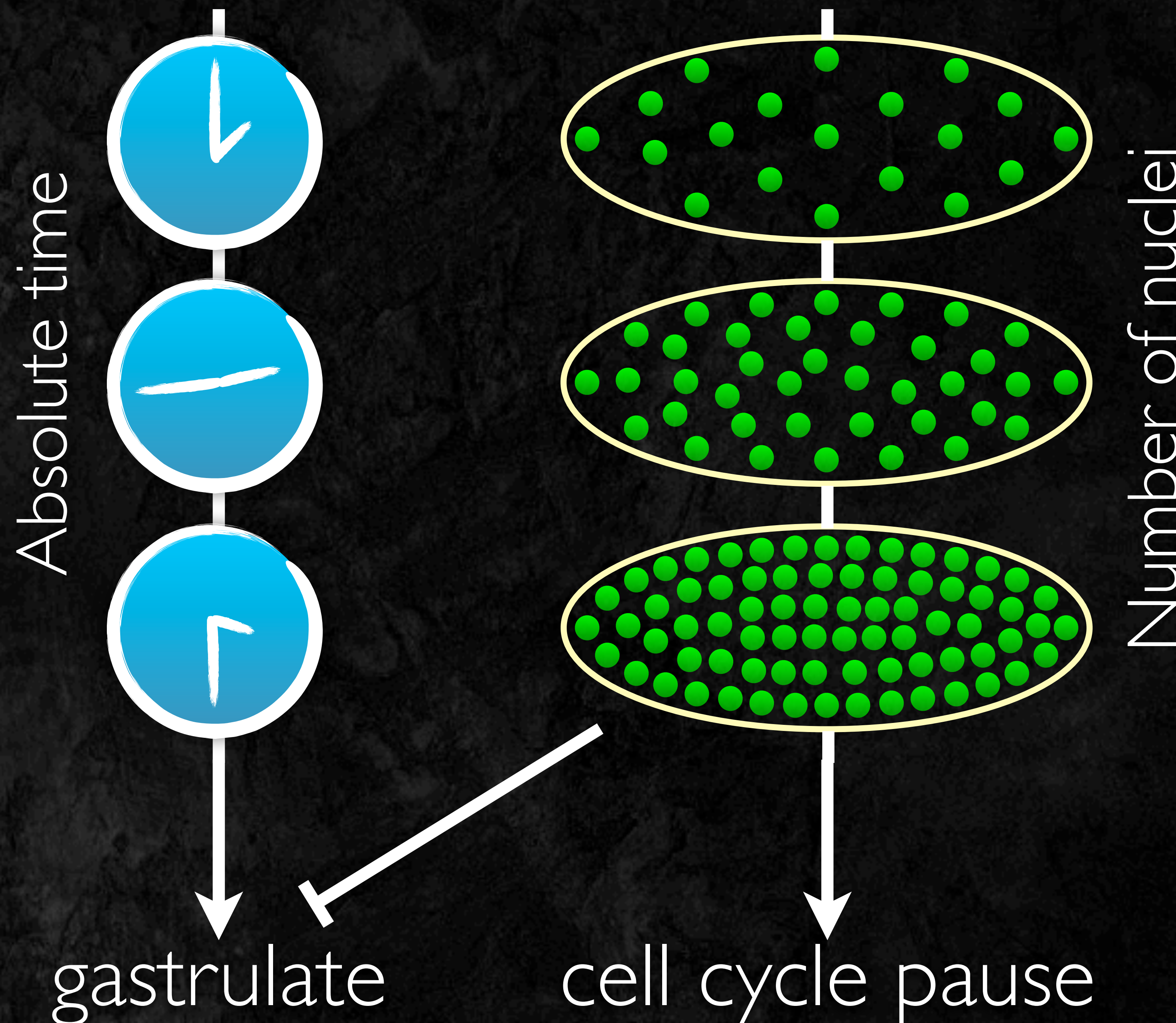
Chromatin markers and late replicating



What times the MBT?

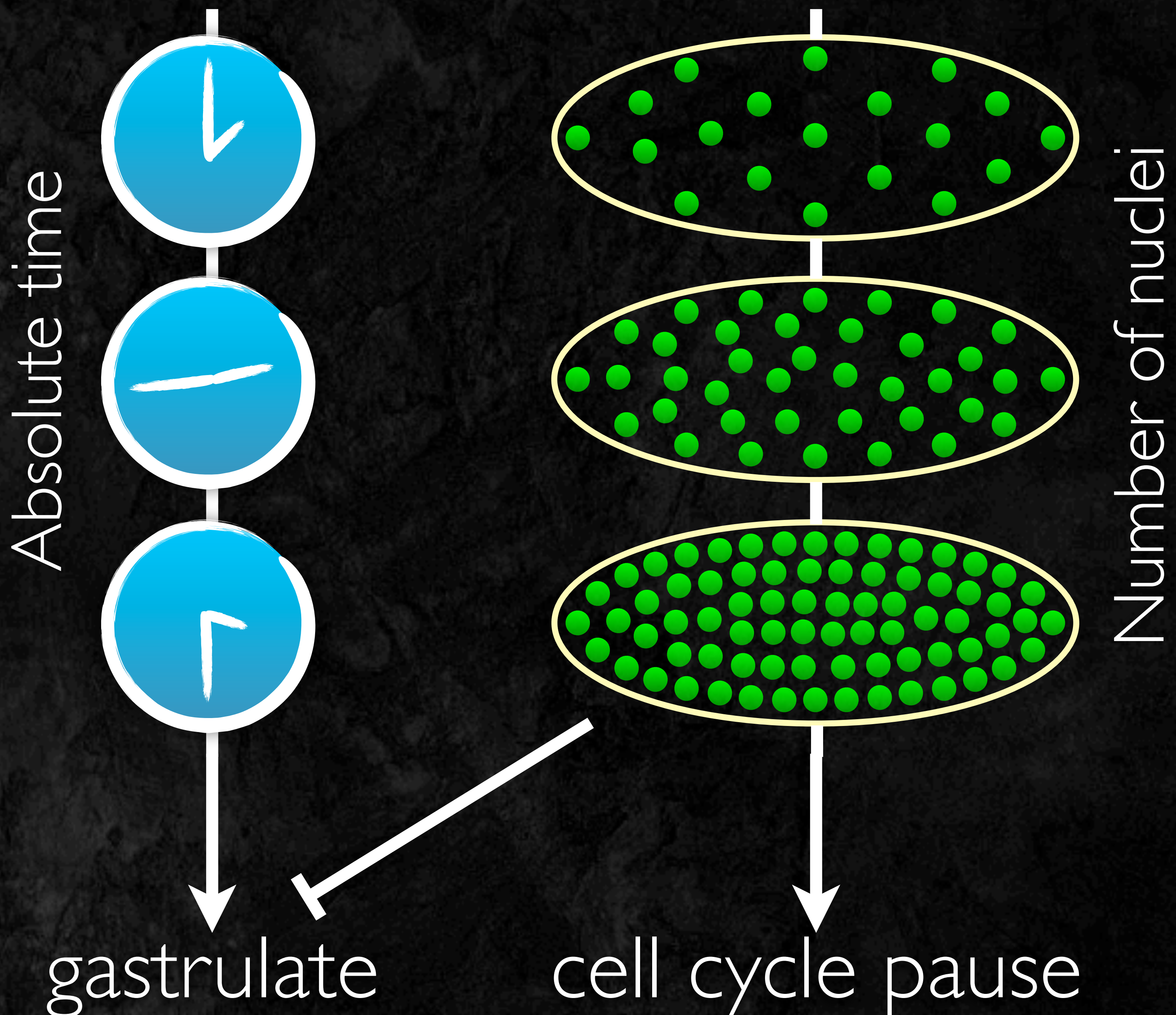


What times the MBT?



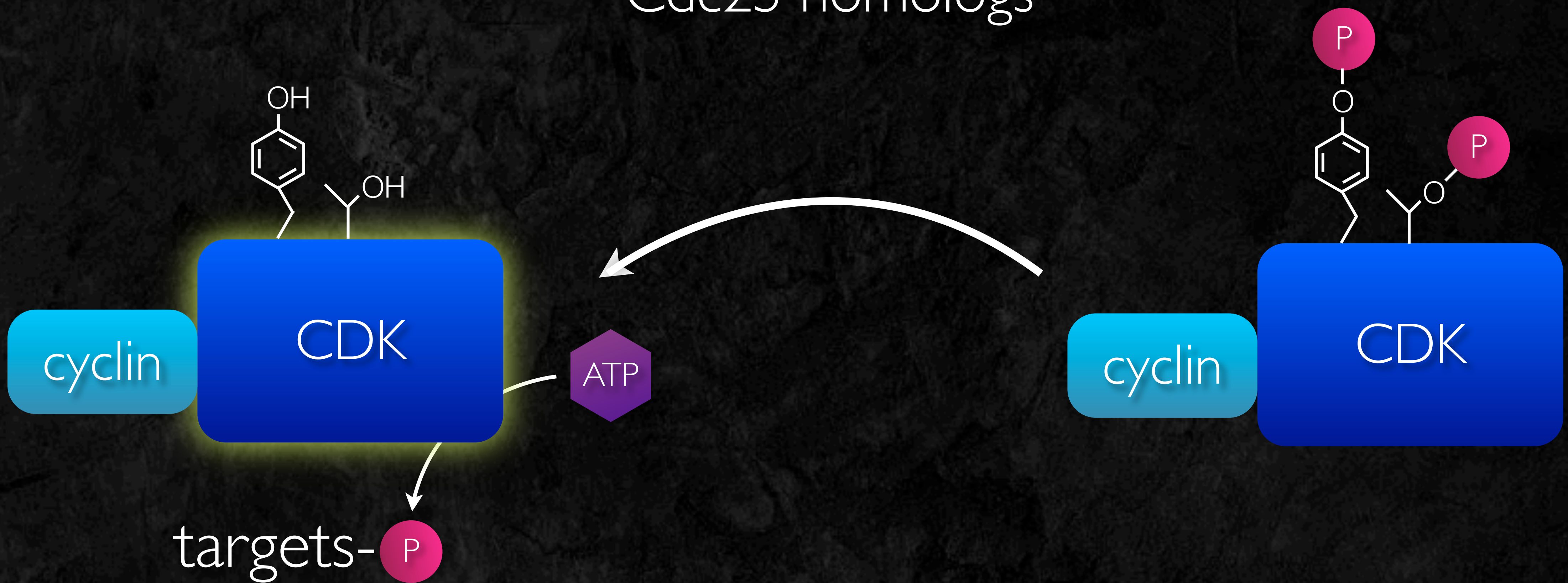
What times the MBT?

Jeff Farrell



Two Cdc25 genes

D. melanogaster's
Cdc25 homologs



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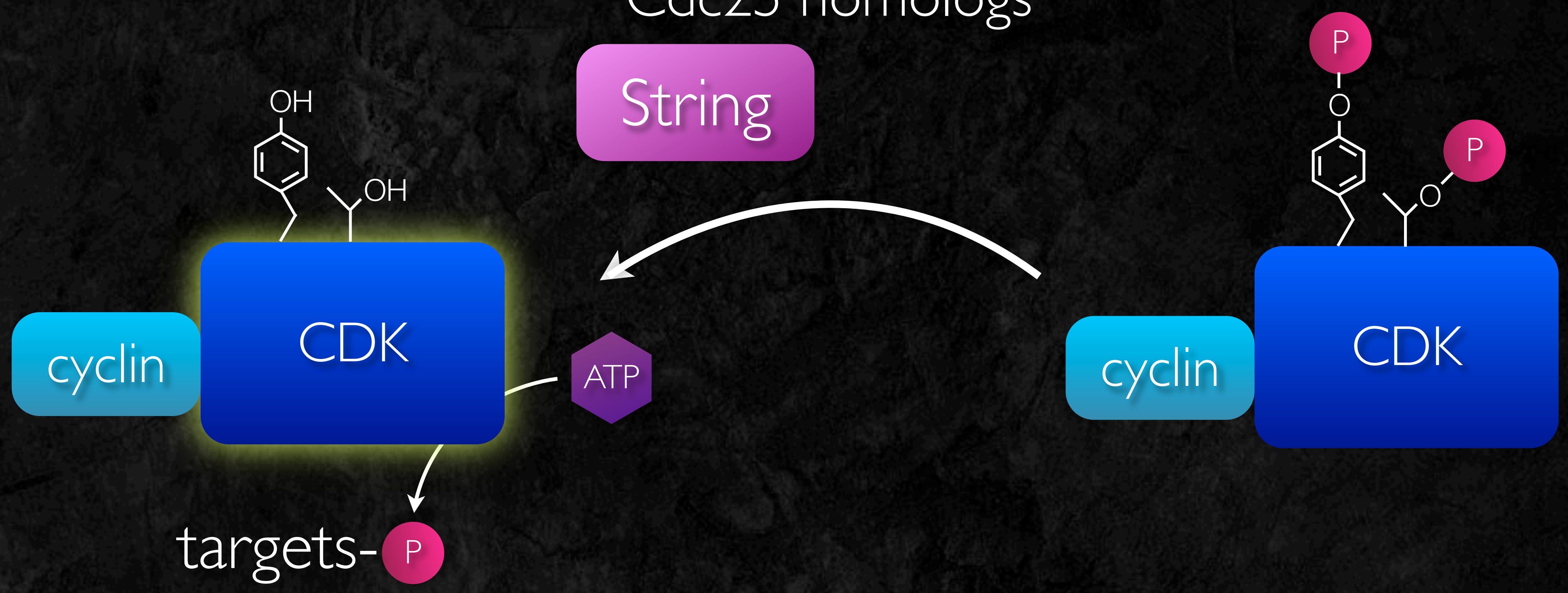
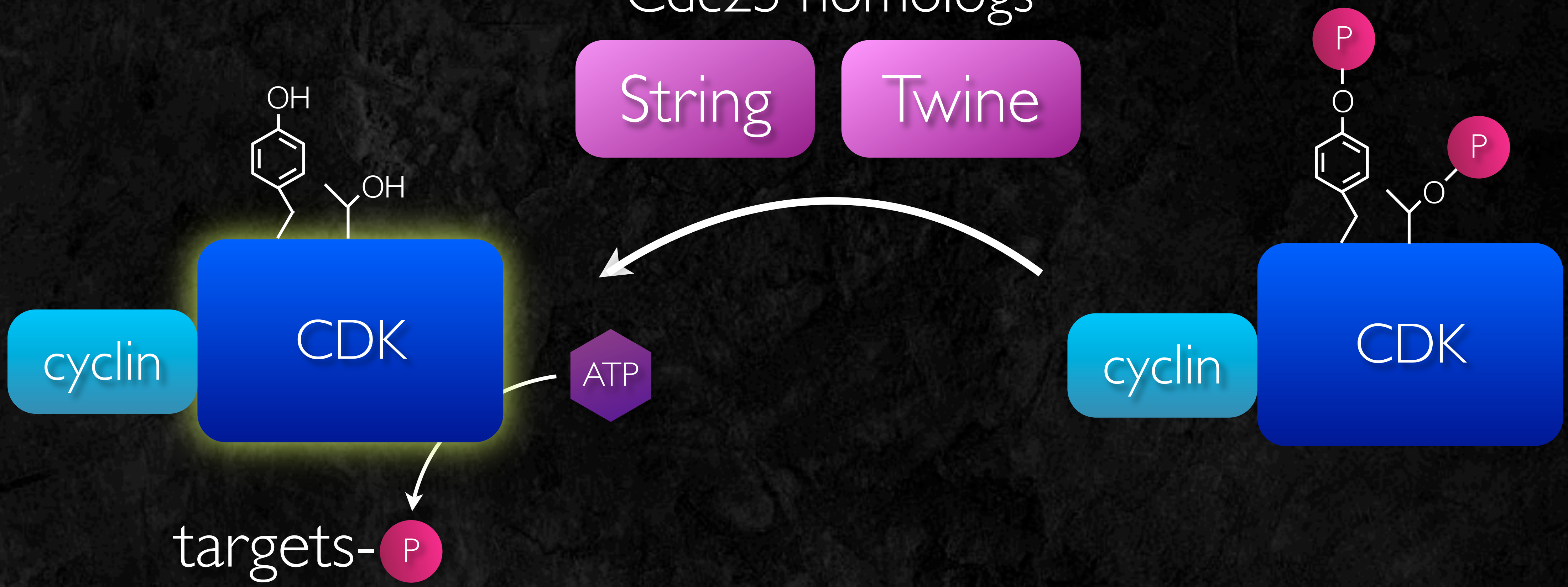


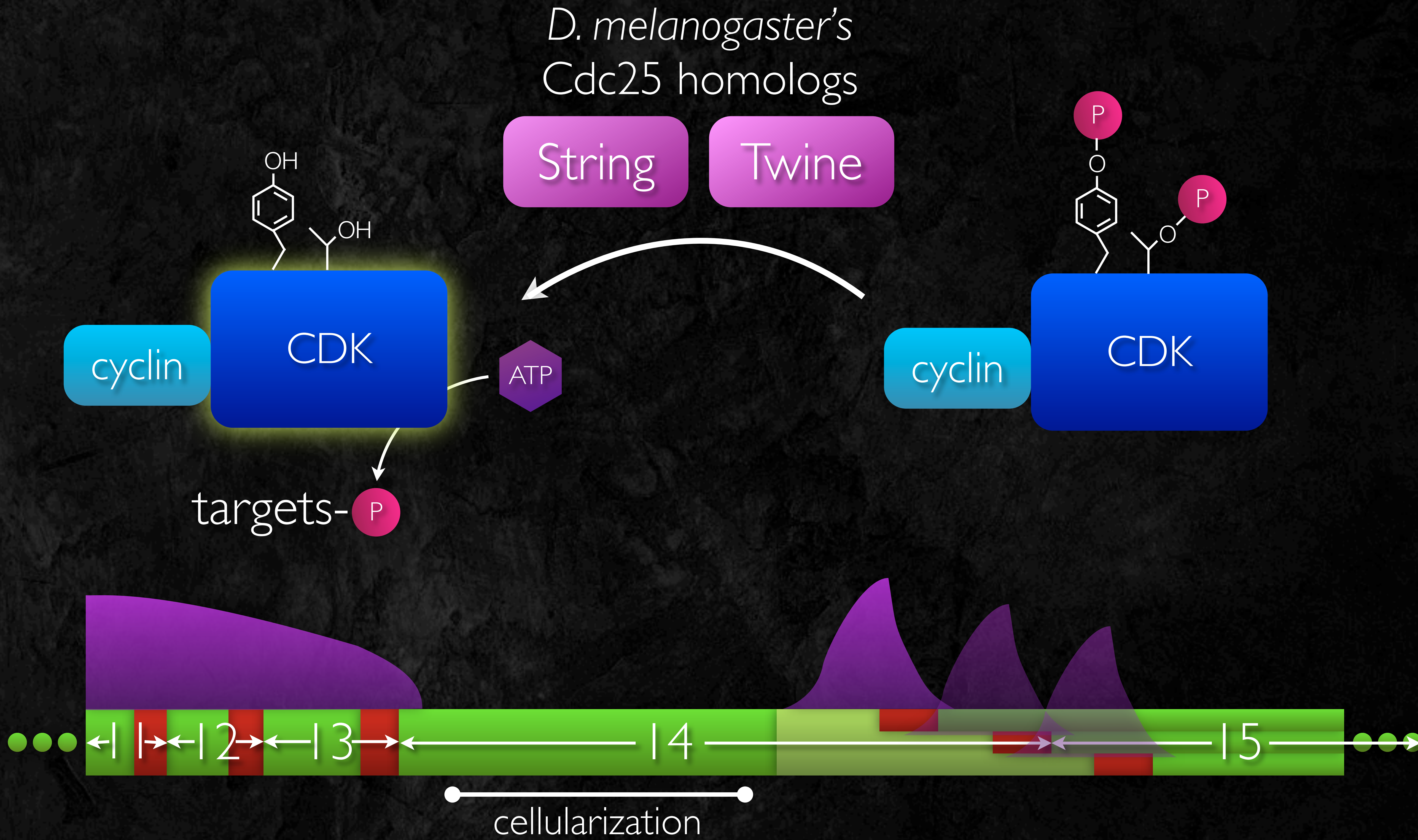
Two Cdc25 genes

D. melanogaster's
Cdc25 homologs

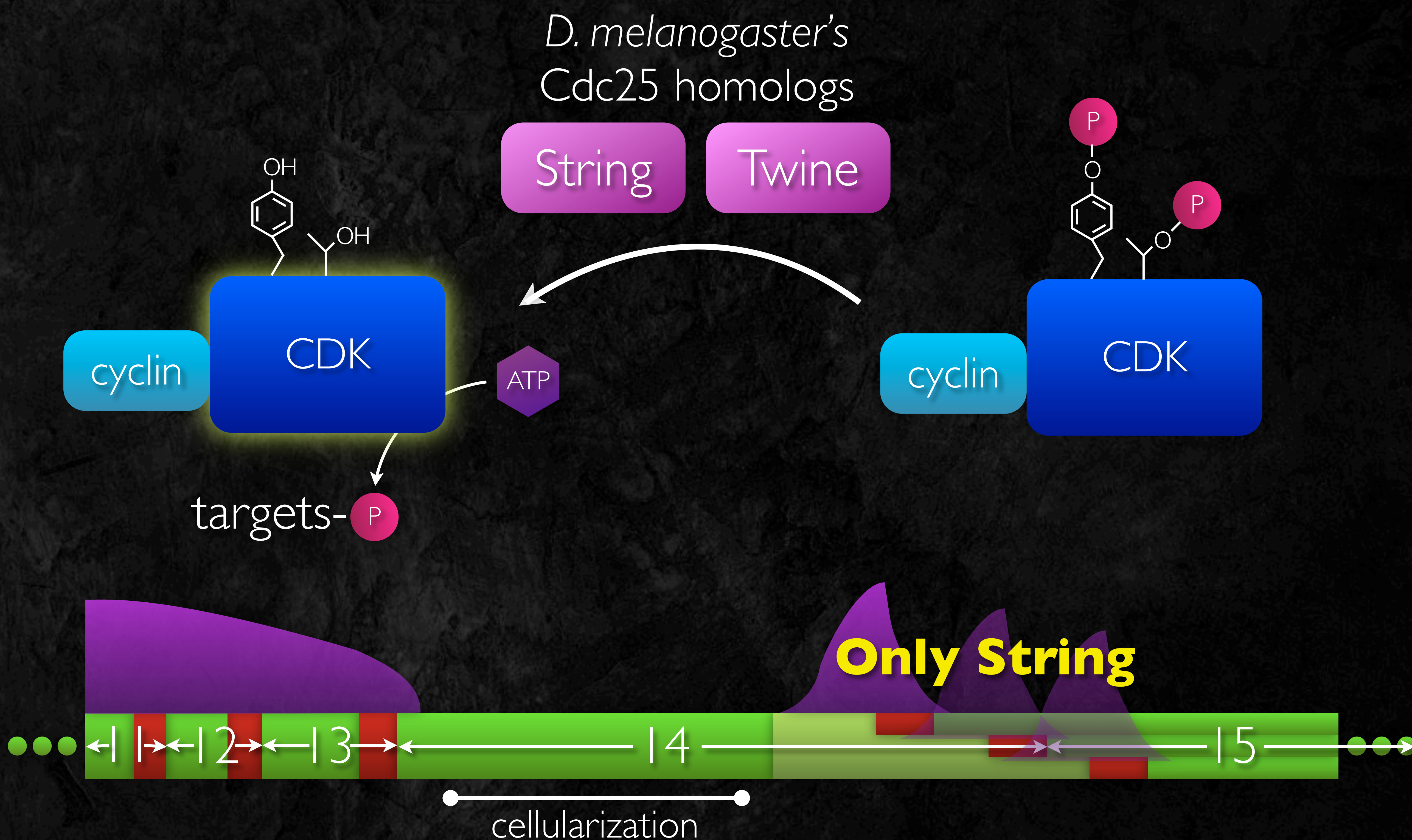
String Twine



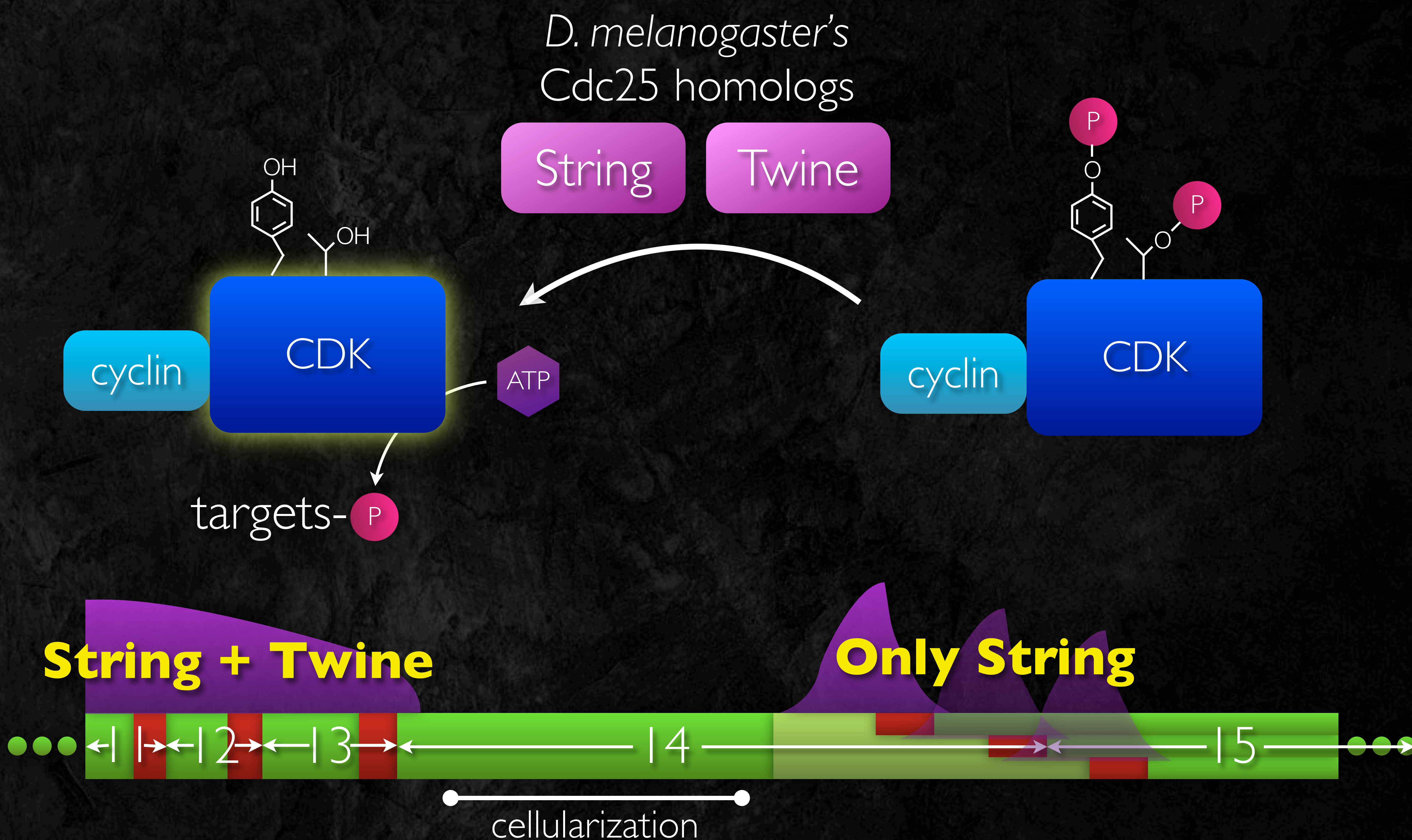
Two Cdc25 genes



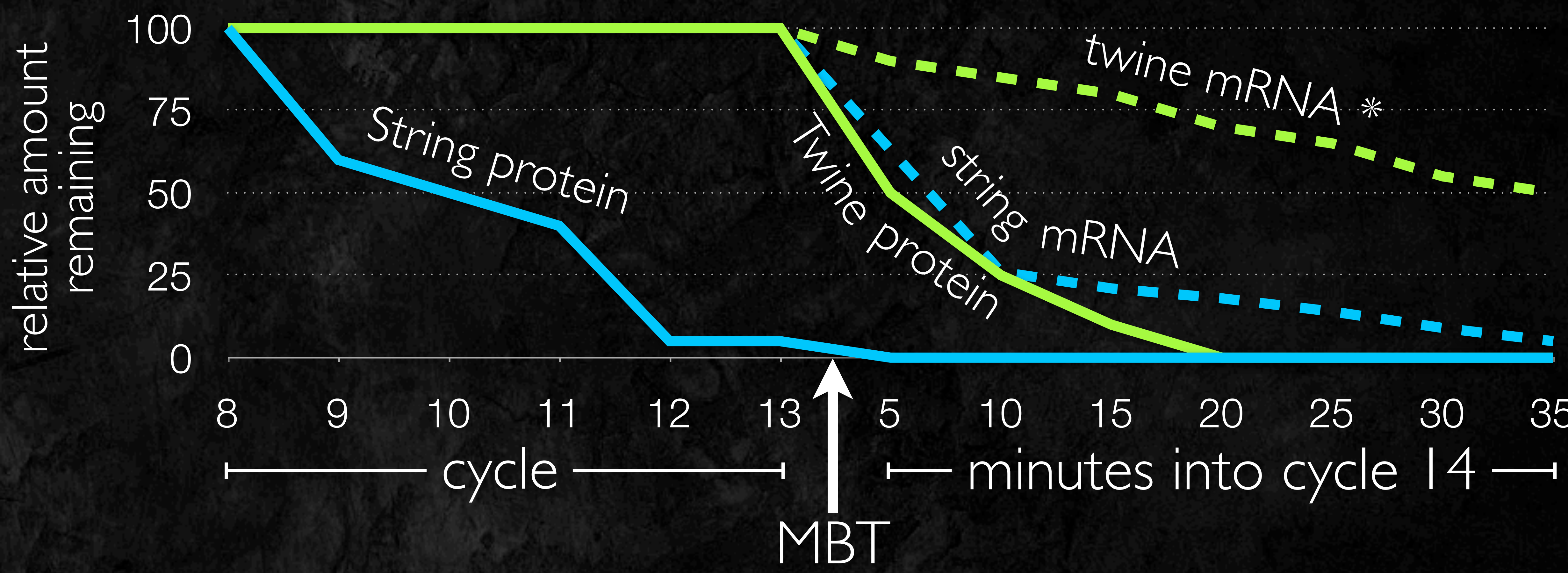
Two Cdc25 genes



Two Cdc25 genes



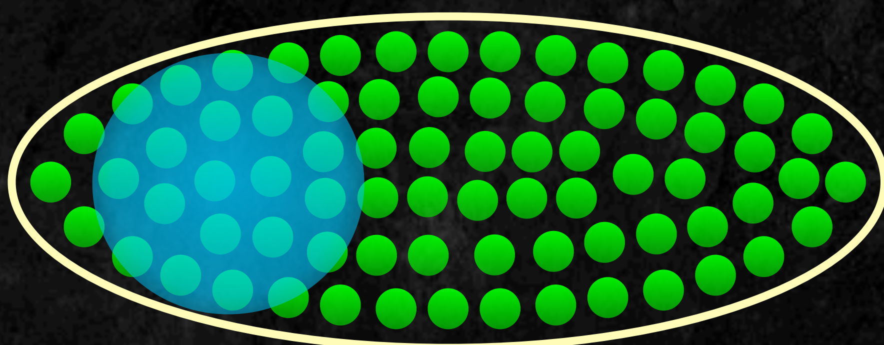
Twine protein is destroyed before its RNA



Focus: Twine protein destruction

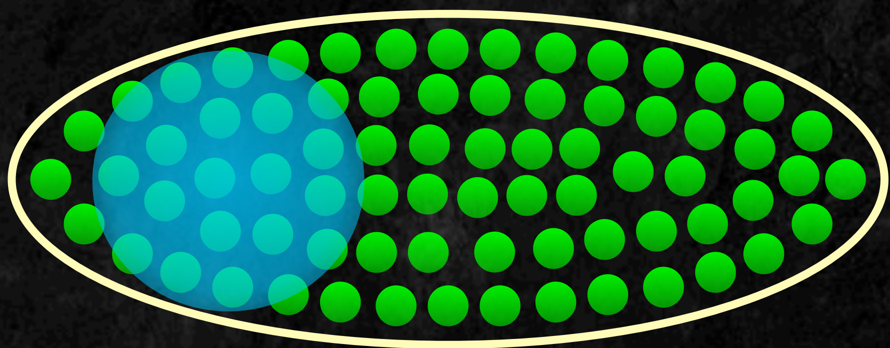
Does Cdc25 destruction require transcription?

Does Cdc25 destruction require transcription?



Inject cycle 13
H2-GFP embryo
with α-amanitin

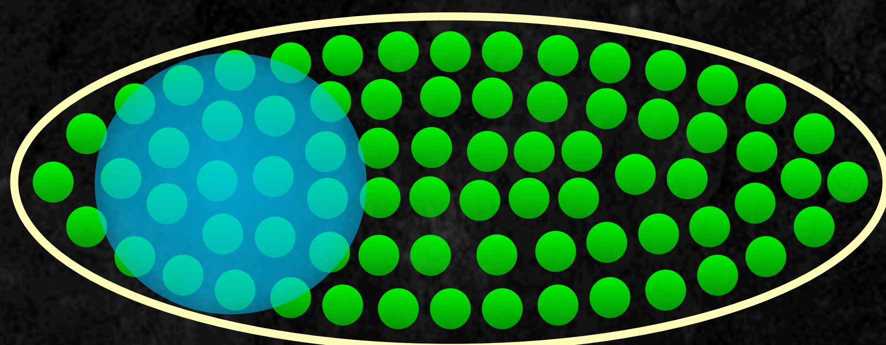
Does Cdc25 destruction require transcription?



Inject cycle 13 H2-GFP embryo with α-amanitin

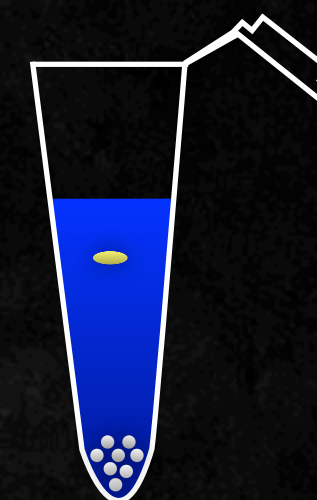
Watch on scope for cycle 14. Count time in cycle 14

Does Cdc25 destruction require transcription?



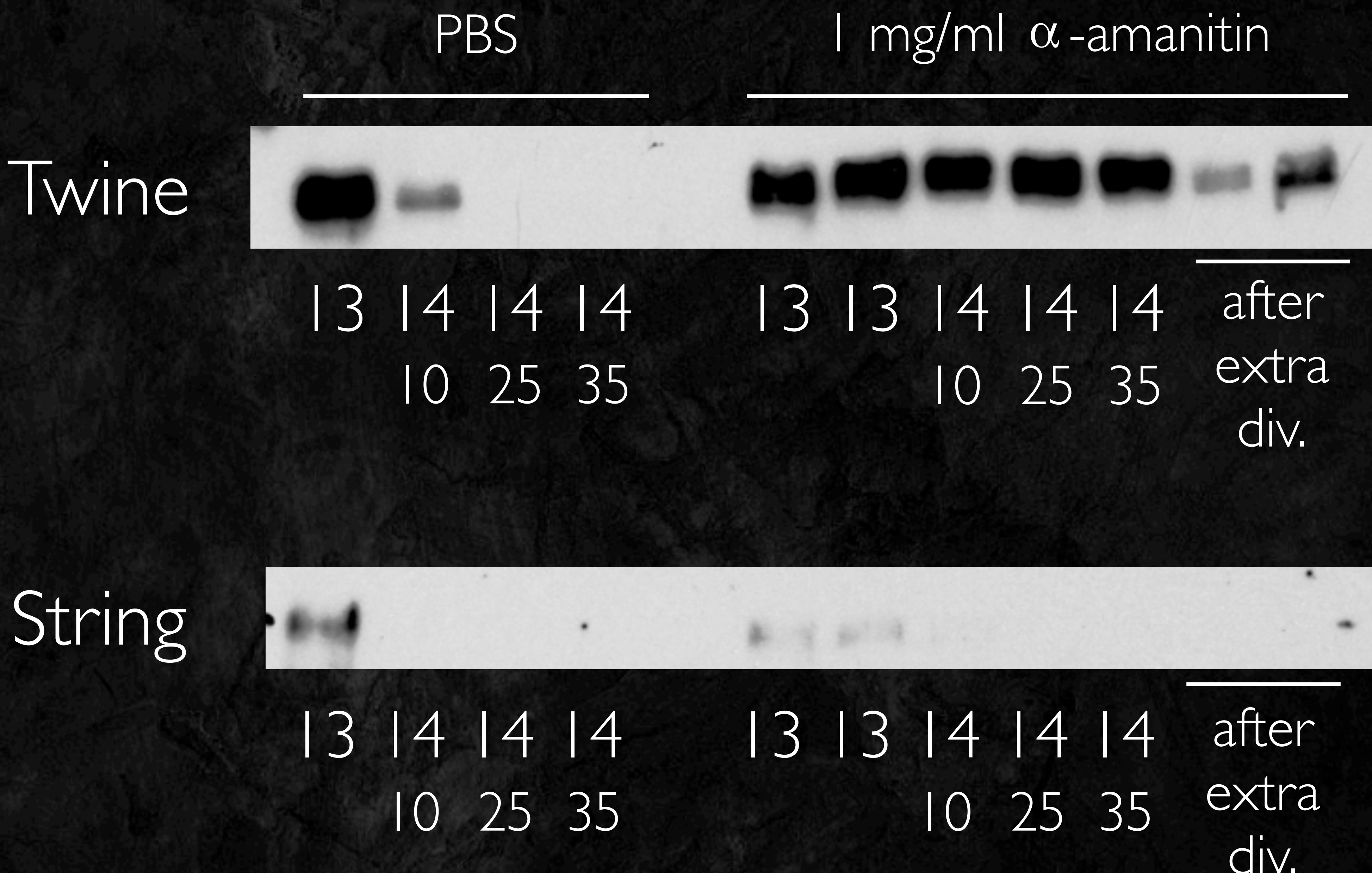
Inject cycle 13 H2-GFP embryo with α-amanitin

Watch on scope for cycle 14. Count time in cycle 14



Retrieve embryo. Smash in SDS. Blot.

Twine destruction inhibited by α-amanitin

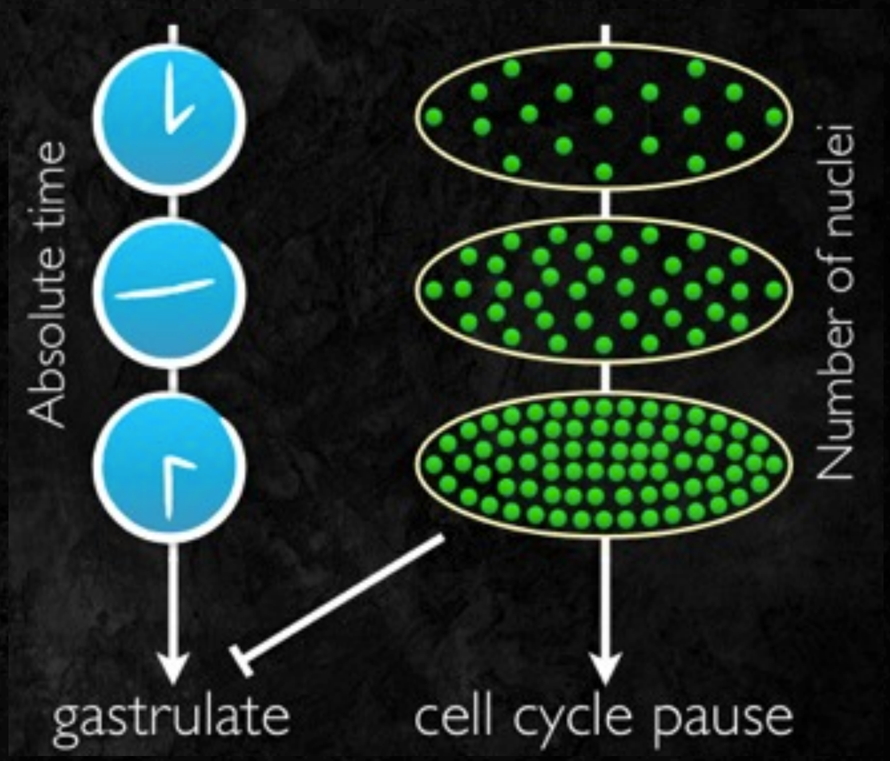


Twine destruction requires new gene expression (zygotic).

Model: A new gene is expressed in the late syncytial cycles that promotes Twine destruction.

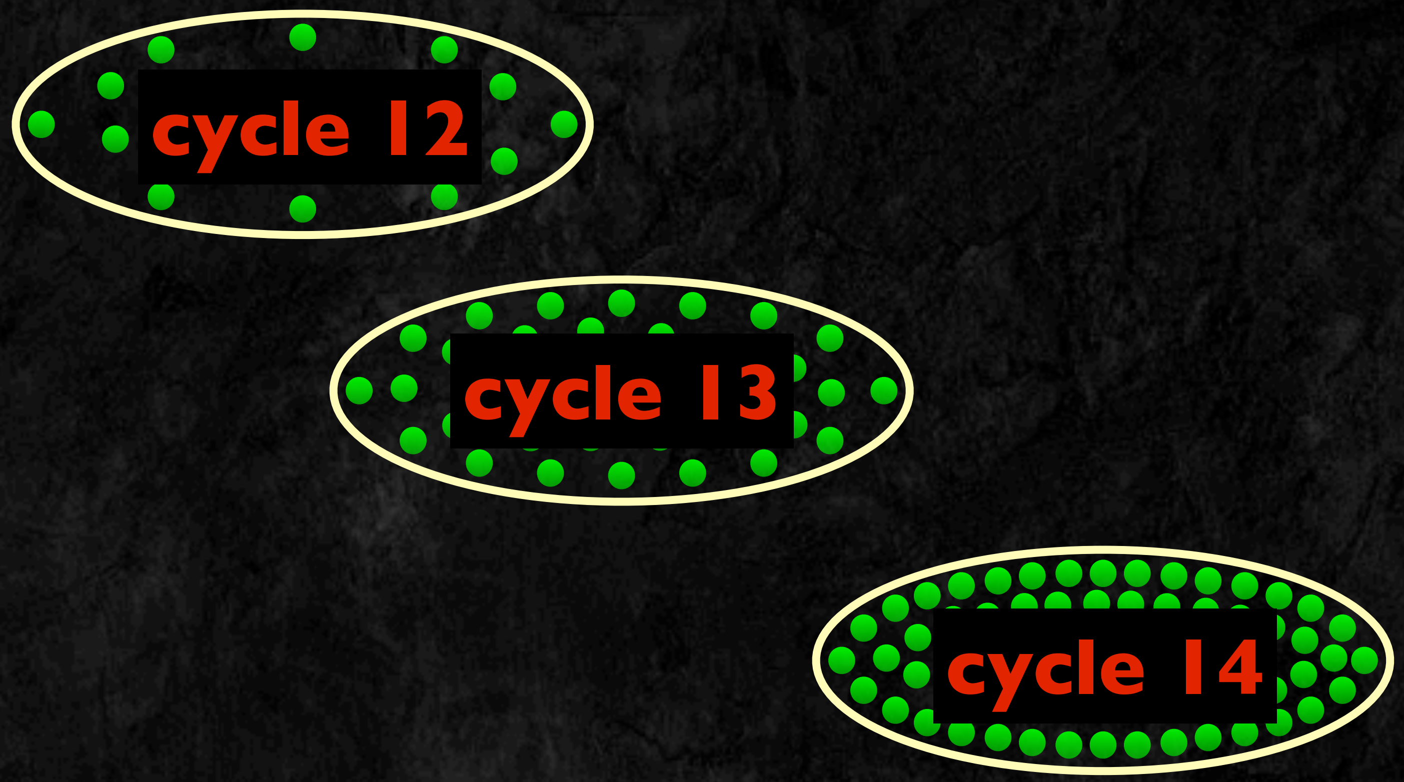
When is this gene expressed?

Is it controlled by time or nuclear density?



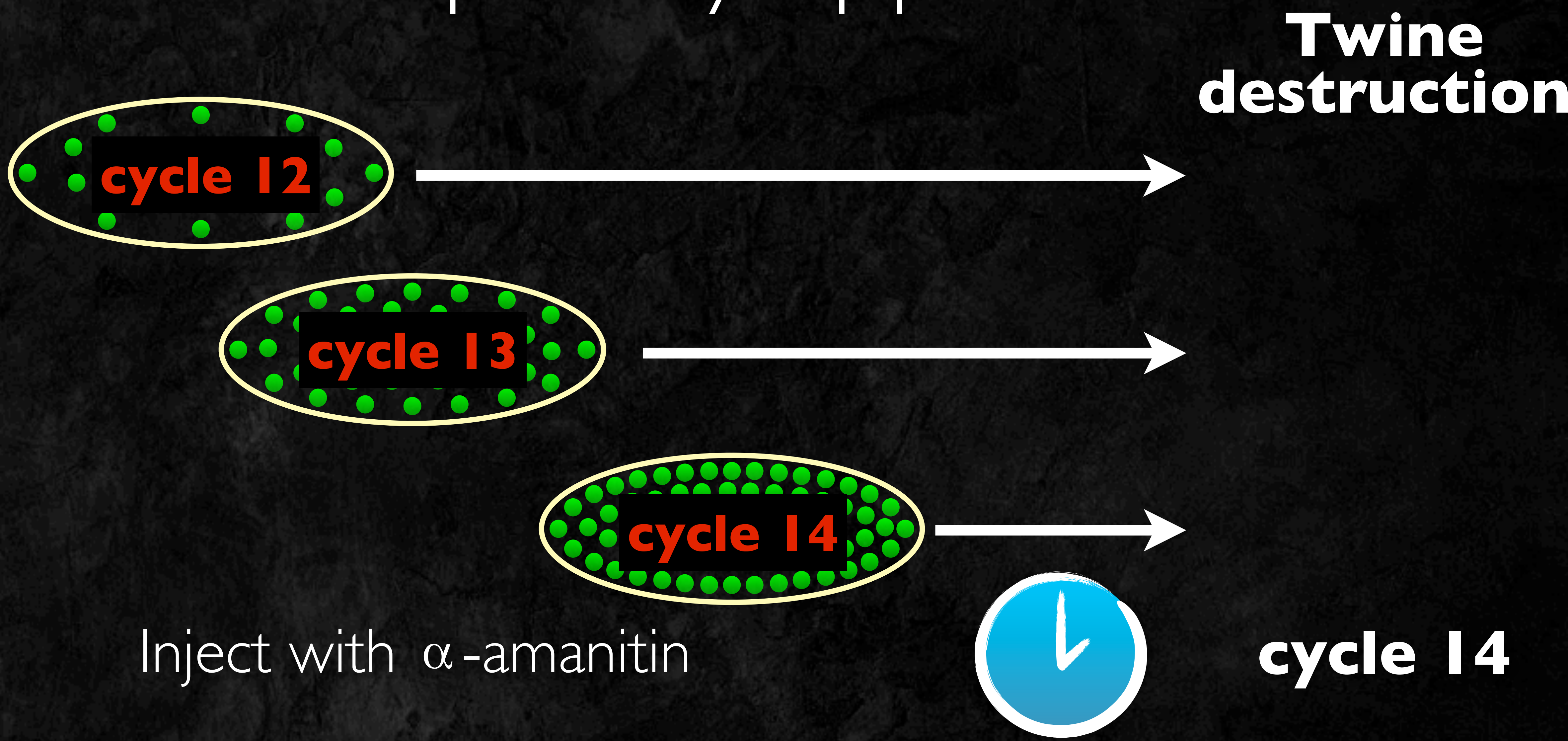
When does destruction capability appear?

When does destruction capability appear?



Inject with α-amanitin

When does destruction capability appear?



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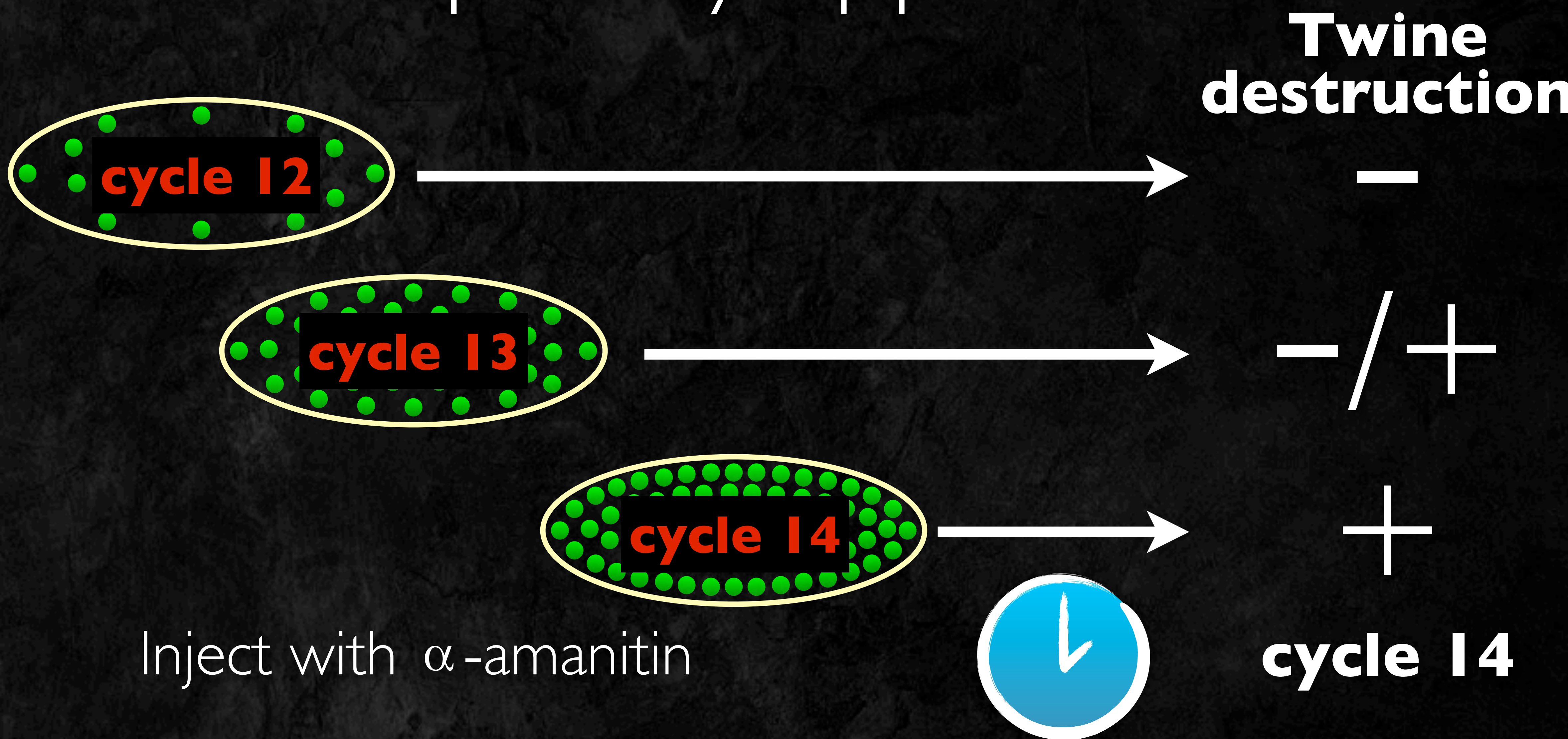

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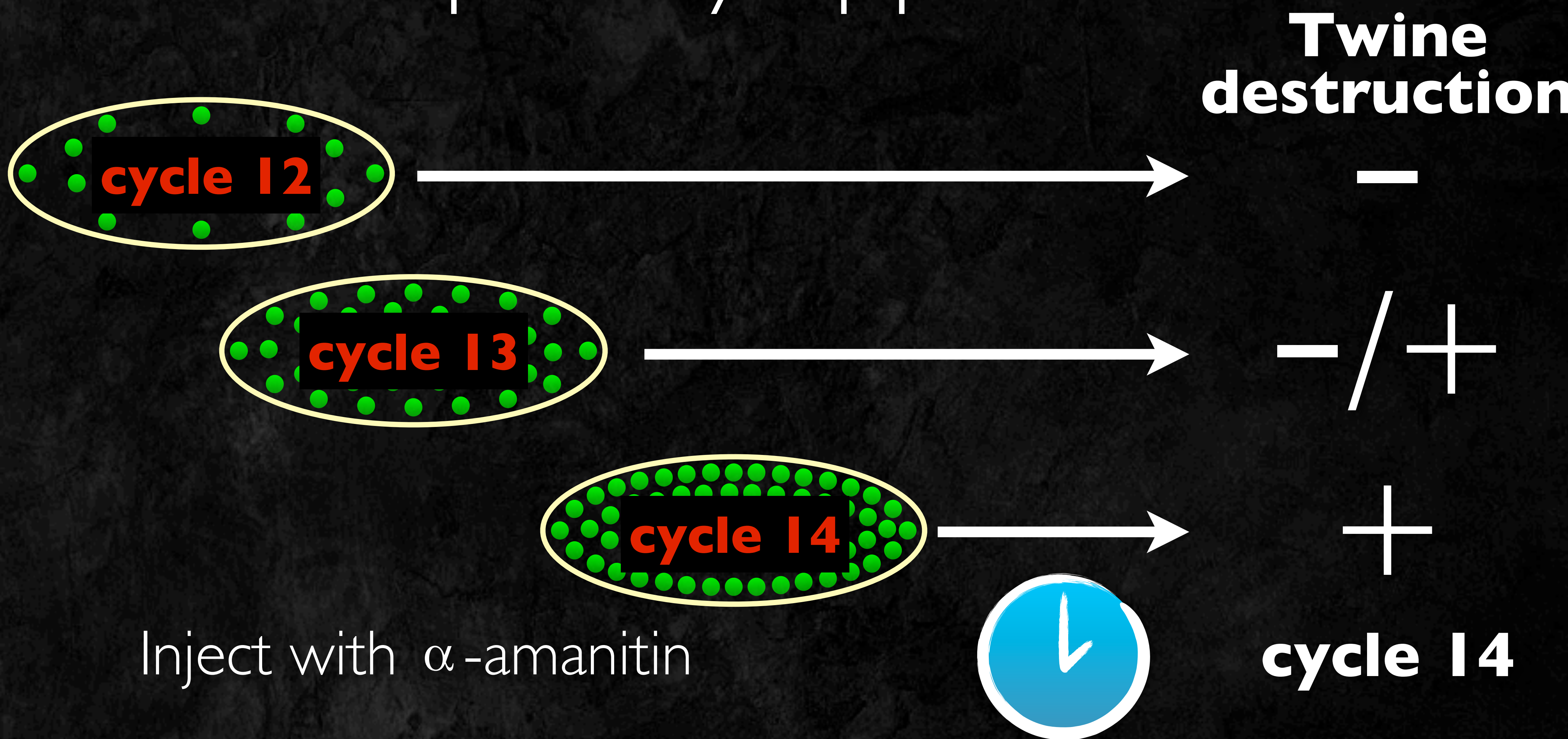
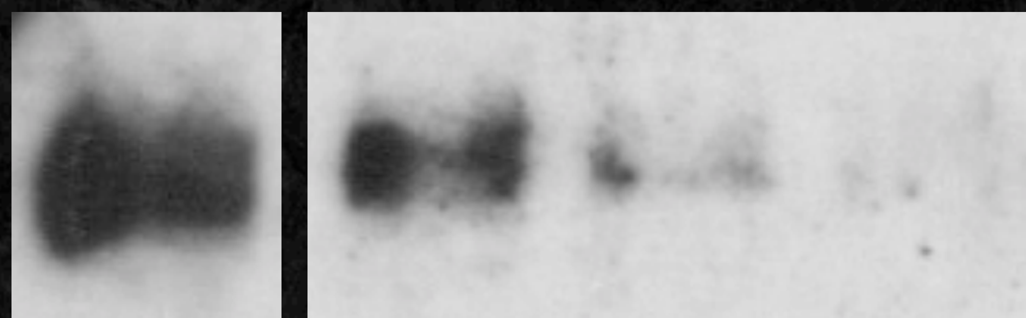


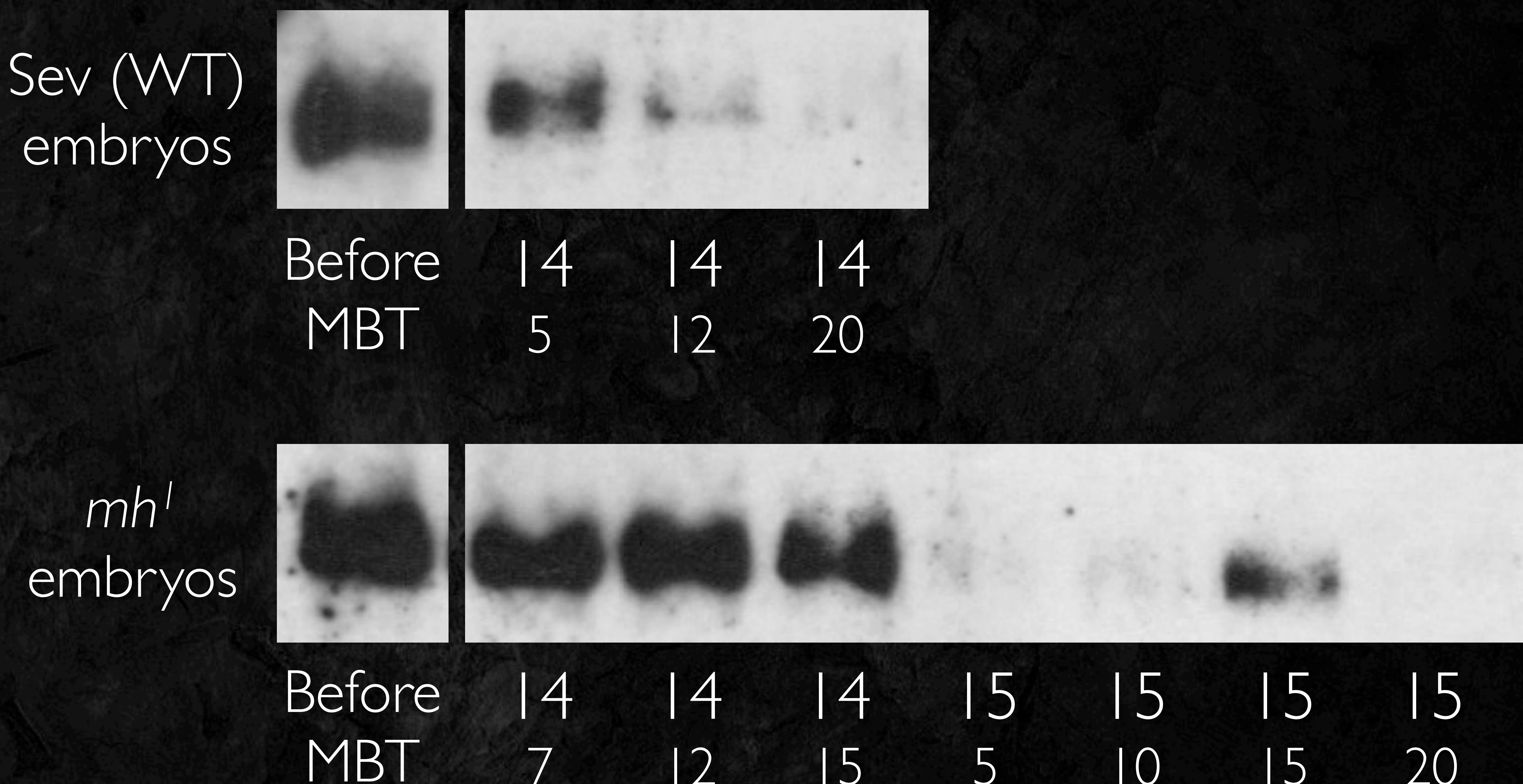
Conclude:

Destruction promoting activity is transcribed in cycle 13

Twine destruction delayed until cycle 15 in haploid embryos

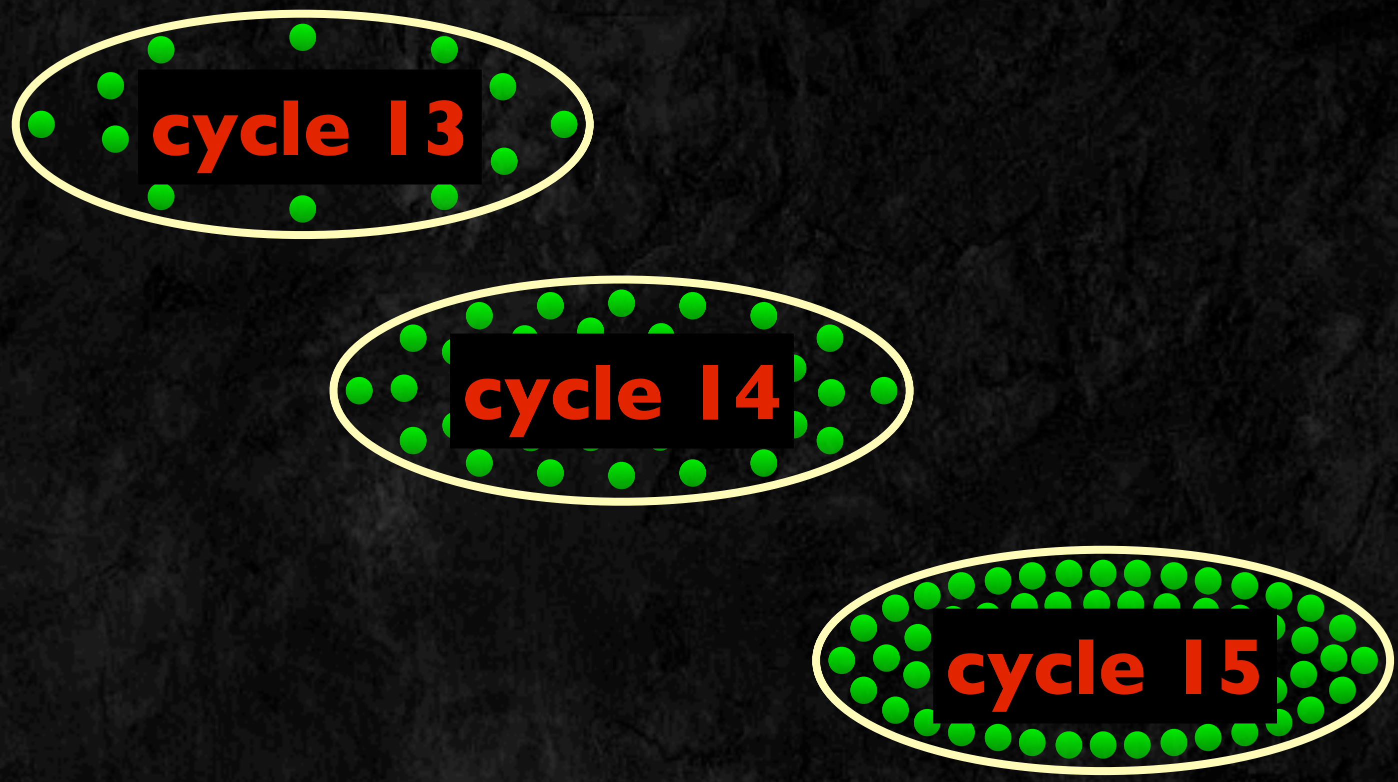


Twine destruction delayed until cycle 15 in haploid embryos



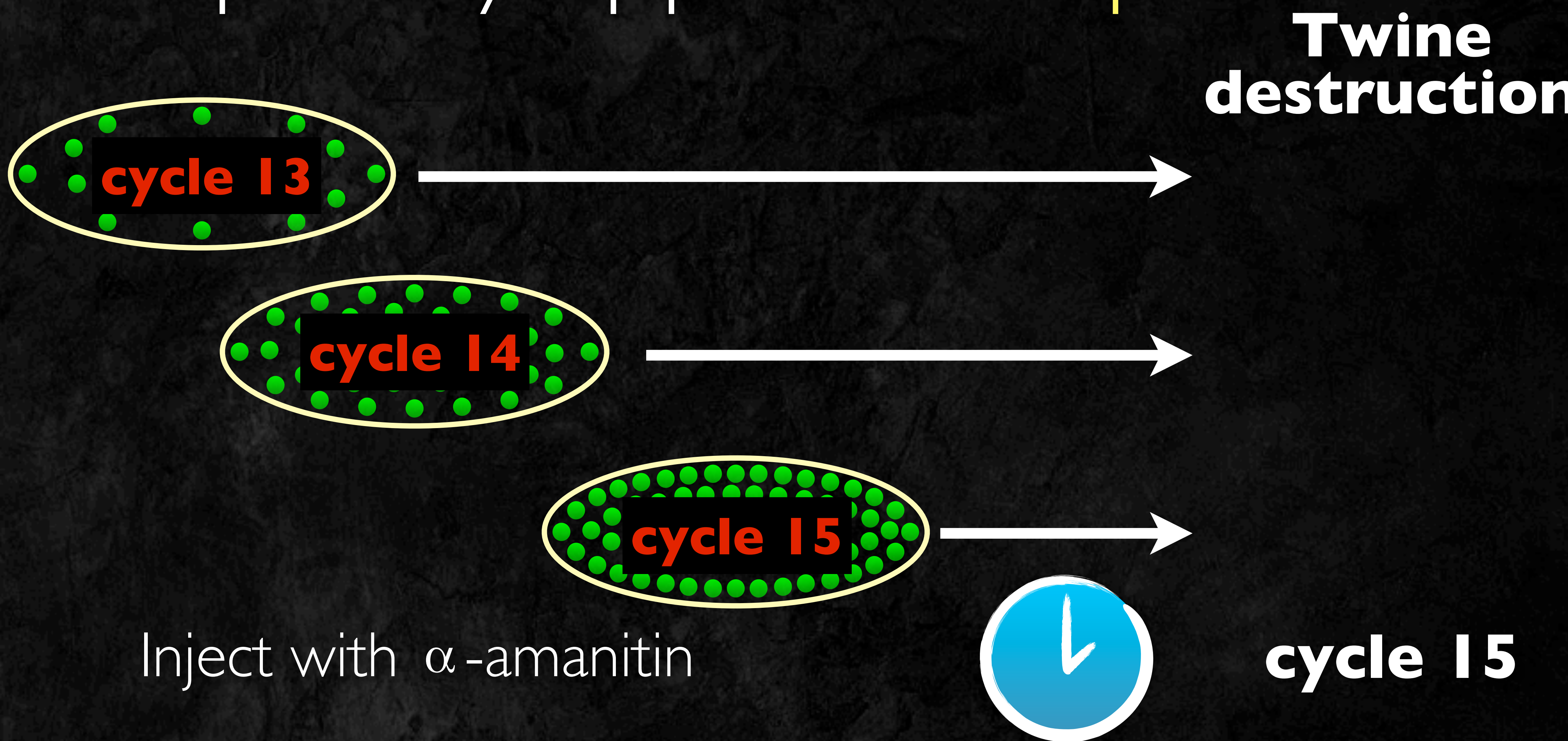
When does destruction capability appear in haploid?

When does destruction capability appear in haploid?

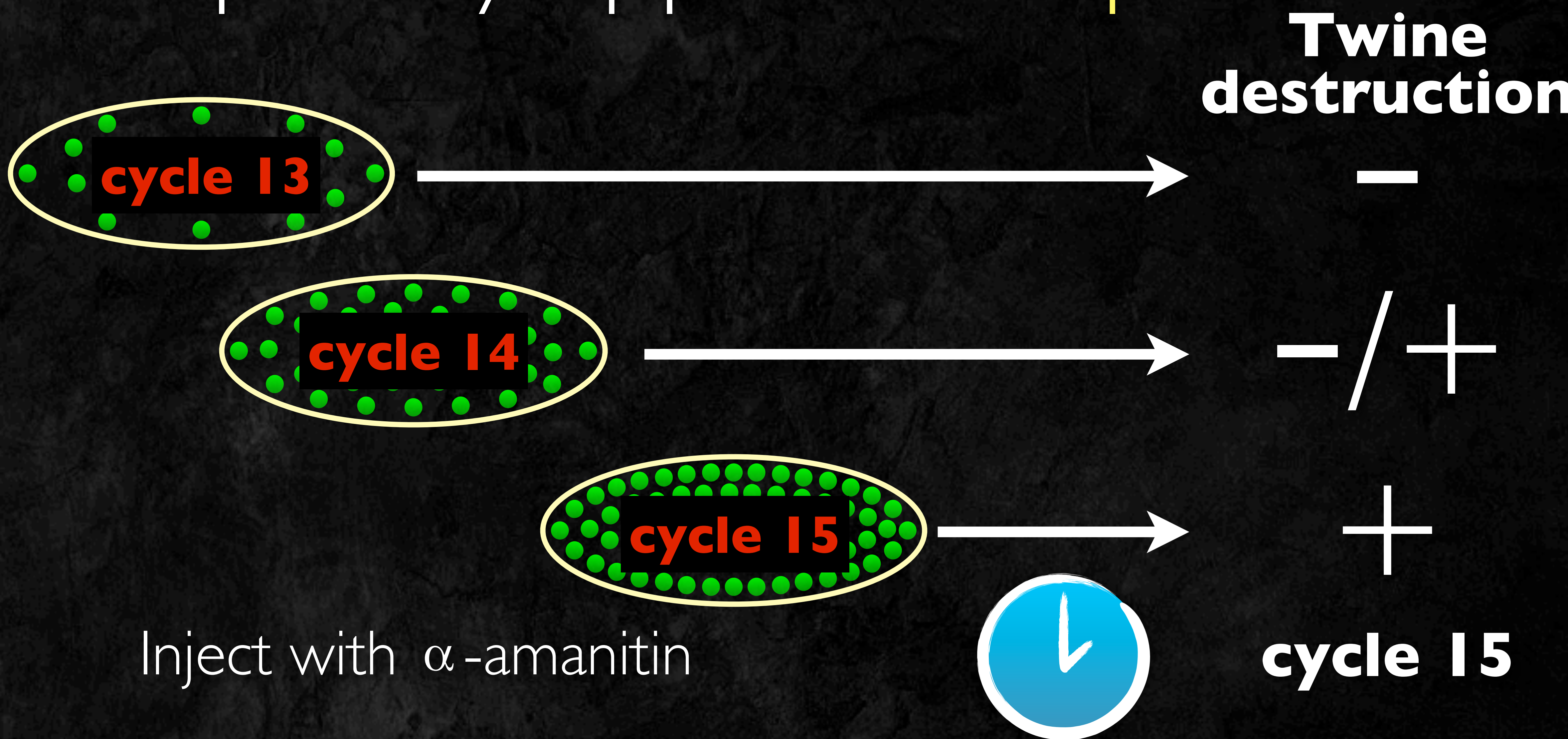


Inject with α-amanitin

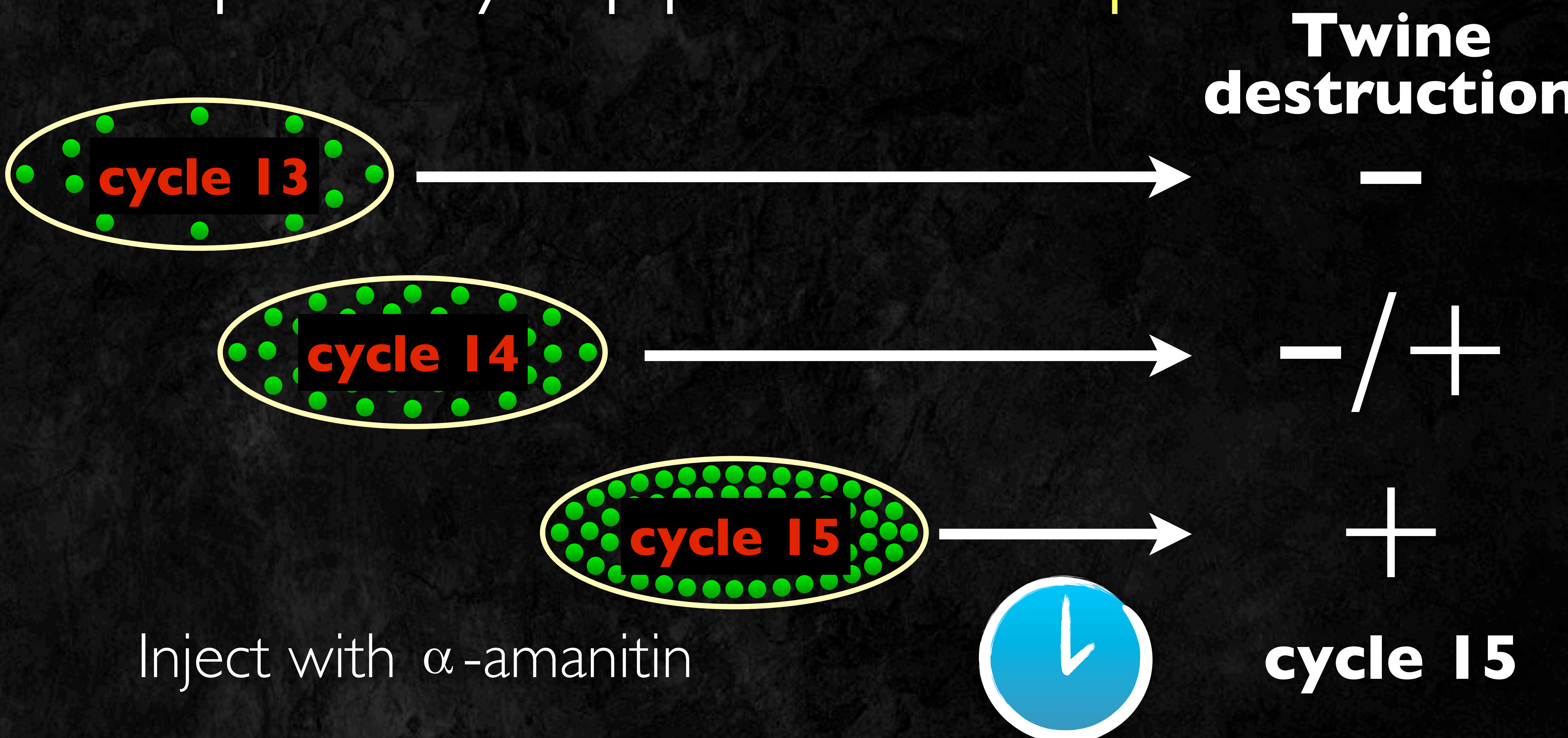
When does destruction capability appear in haploid?



When does destruction capability appear in haploid?



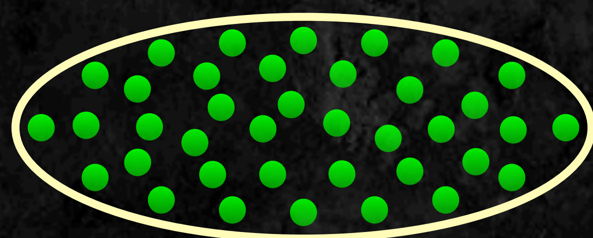
When does destruction capability appear in haploid?



Conclude:

Time of transcription of destruction activity depends on ploidy.

Model



Nuclear density → transcription gene x → x degrades Cdc25 Twine

- S phase prolongation
- introduces G2

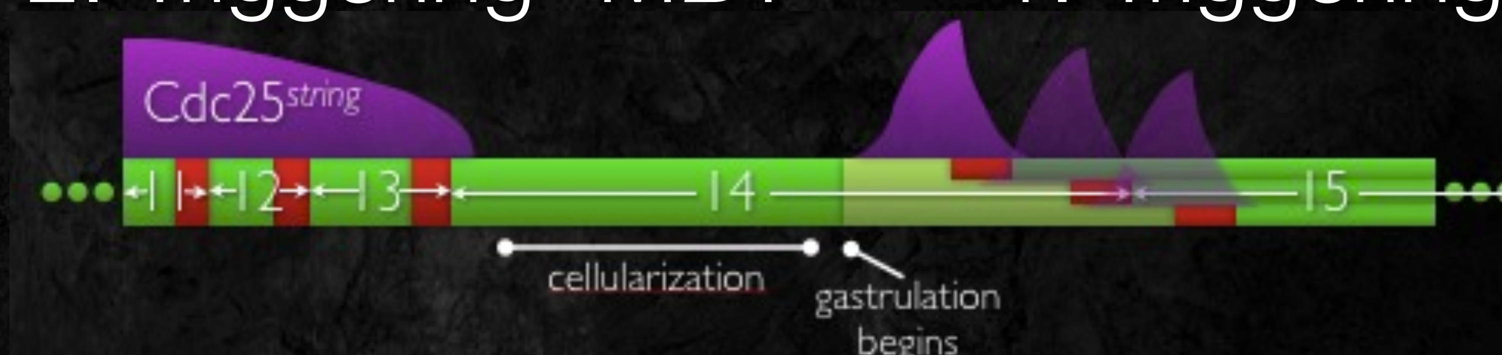
looking for gene x

The embryo runs on tight schedule

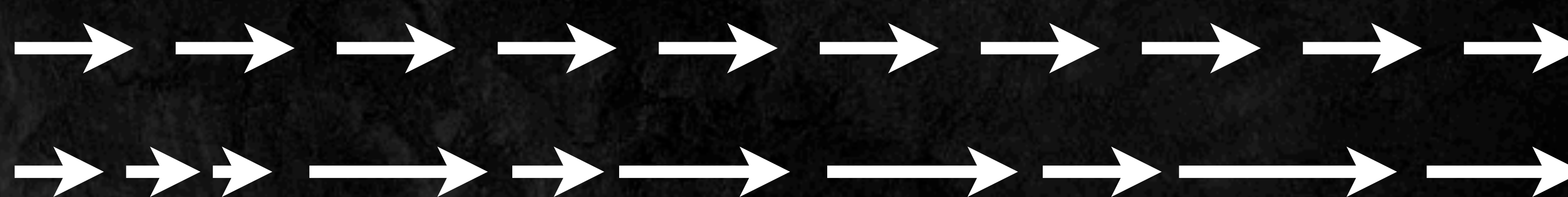
Timed events need a clock and a trigger

Changes in Cdc25 as a trigger

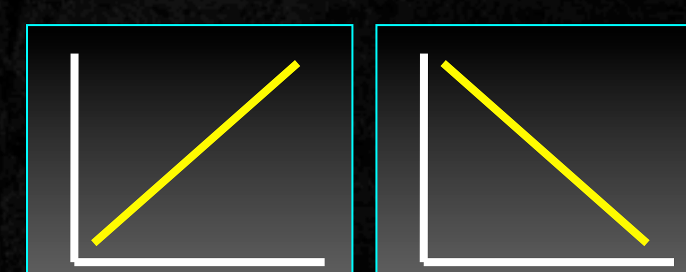
2. Triggering "MBT" 1. Triggering M



Clock = ?



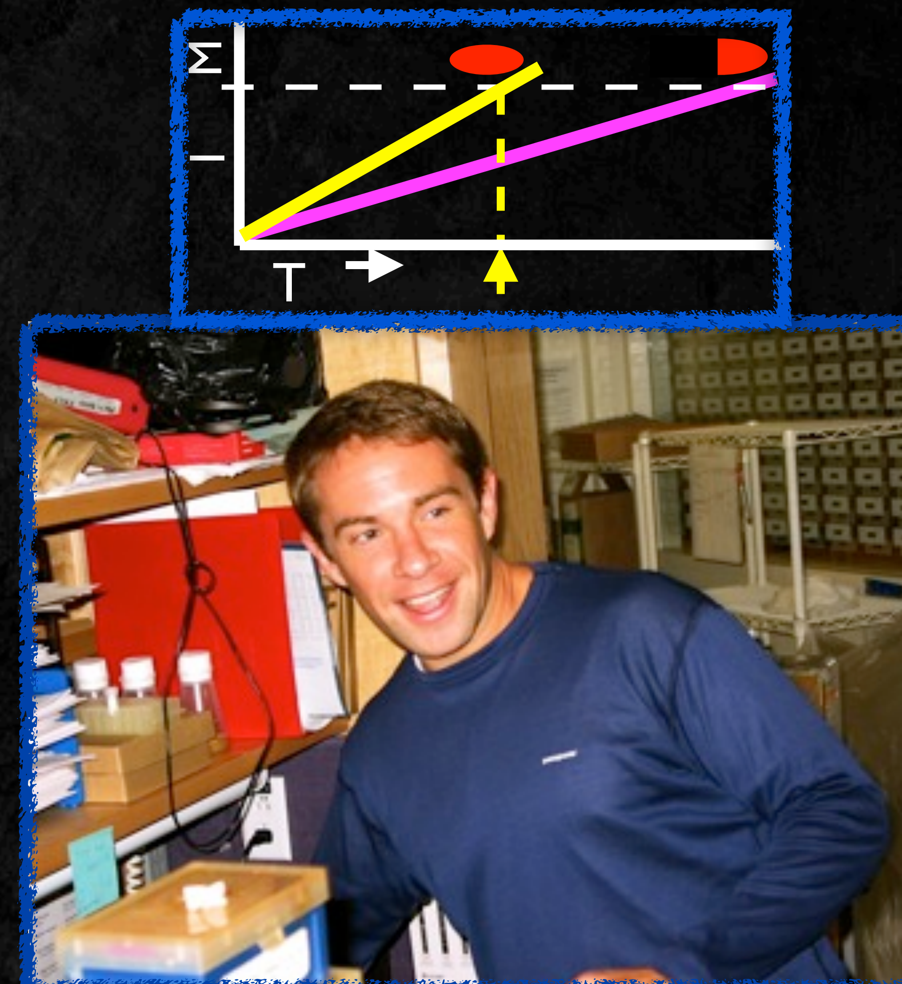
Propose: Egg begins with huge mitotic drive that declines during early cycles triggering transcription and Cdc25 destruction at cycle 14.



San Francisco from Mission Bay, UCSF

Christine Lehner

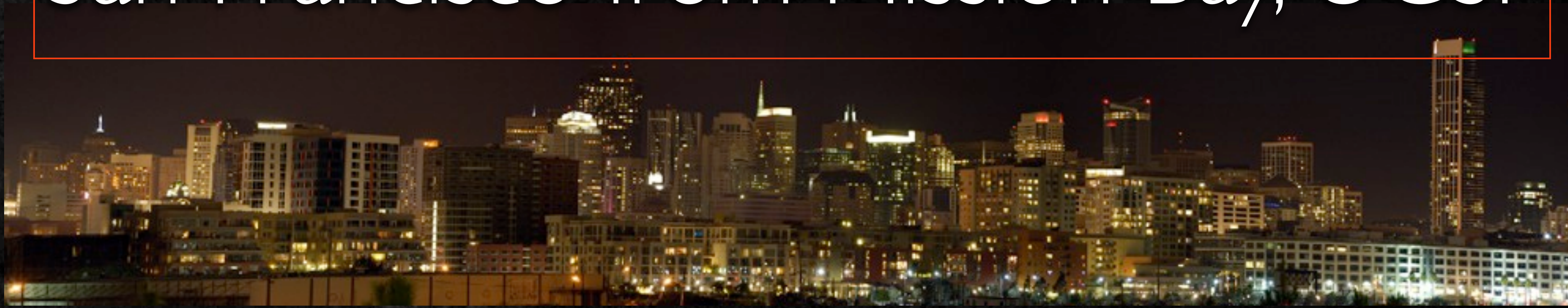
Bruce Edgar



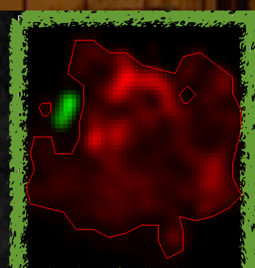
Mark McCleland

MY EXs

San Francisco from Mission Bay, UCSF



San Francisco from Mission Bay, UCSF



Tony Shermoen

Jeff Farrell