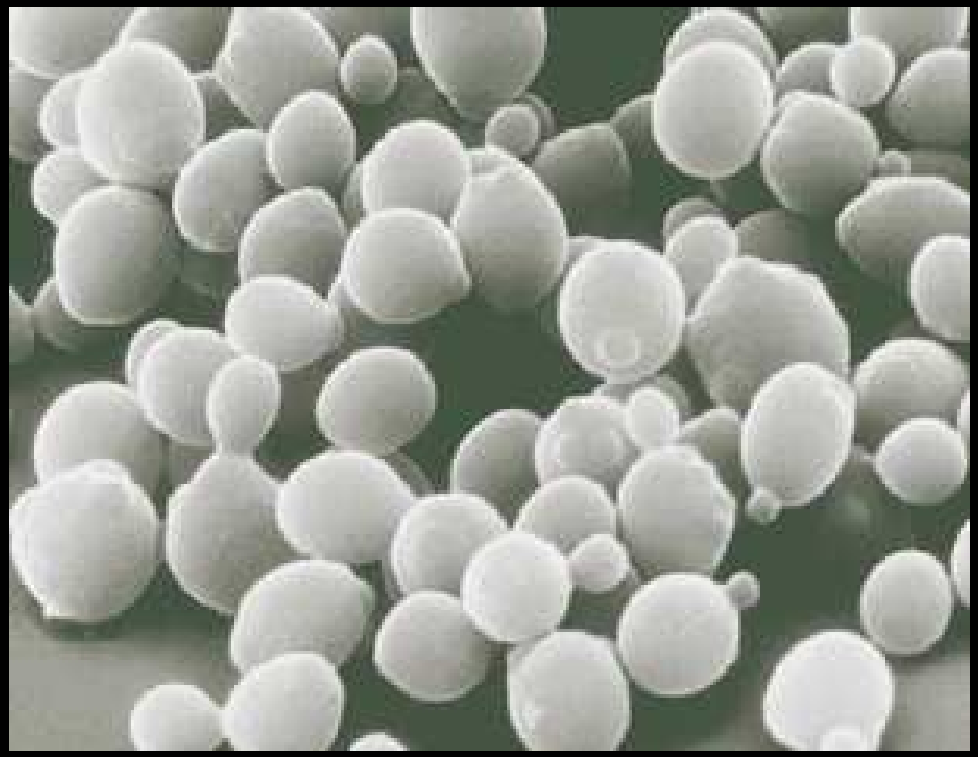
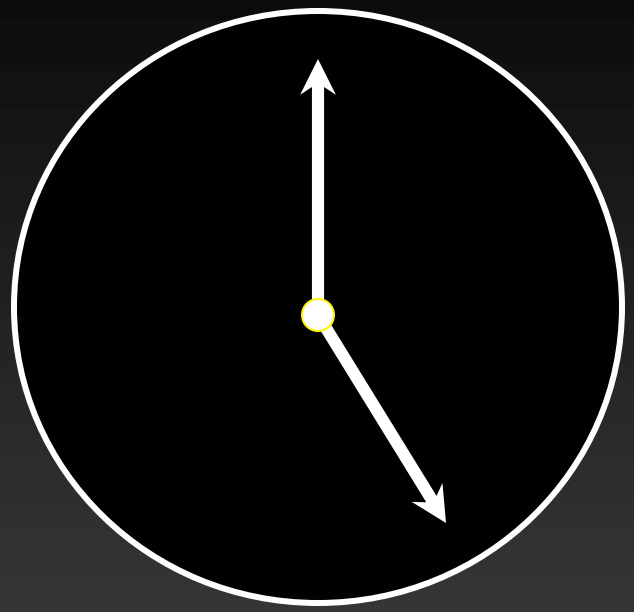
Cycling Without Cyclins: New Views on the Oscillator

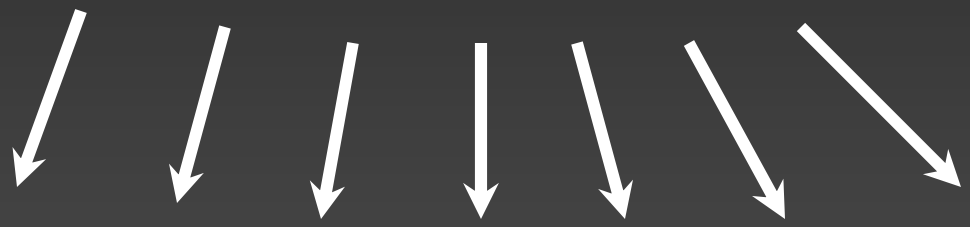


Steve Haase
Duke Center for Systems Biology

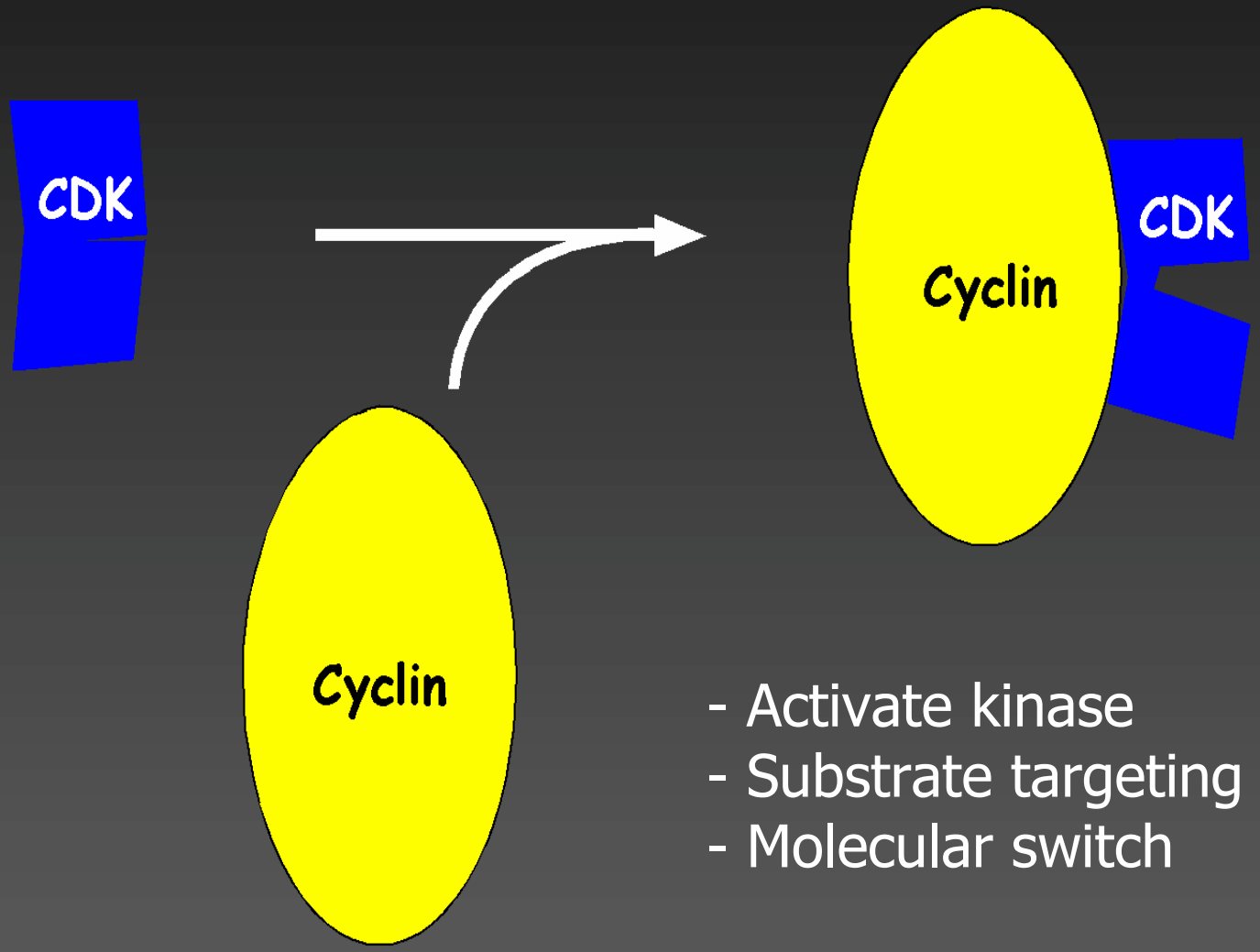
Fields Institute, 2010



Cyclin/CDK



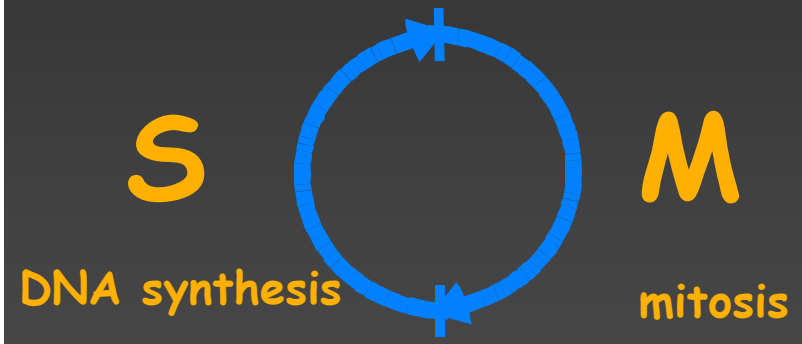
Cyclin Dependent Kinase (CDK)



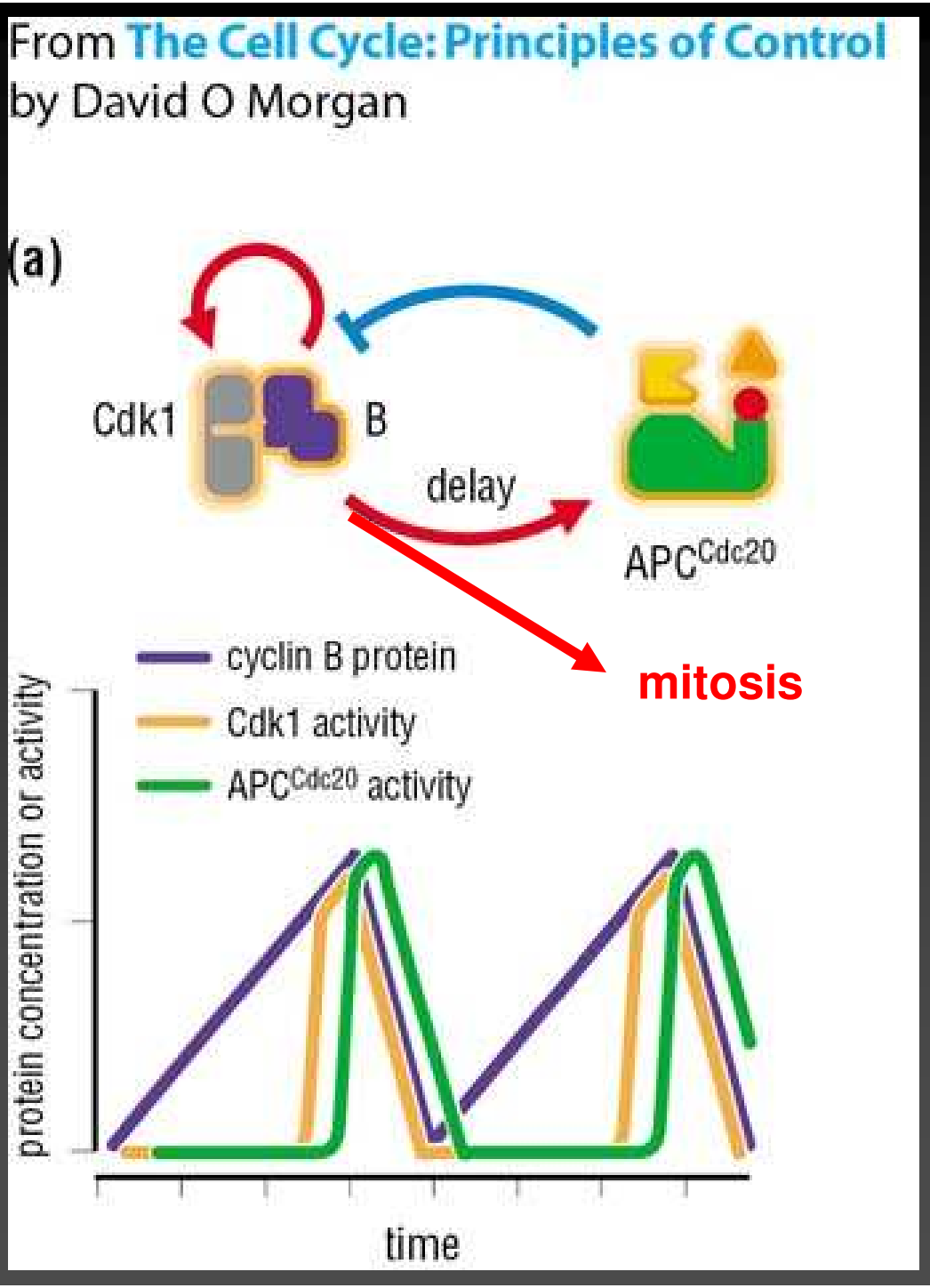
- Activate kinase
- Substrate targeting
- Molecular switch

A simple cell-cycle oscillator model:

embryonic systems



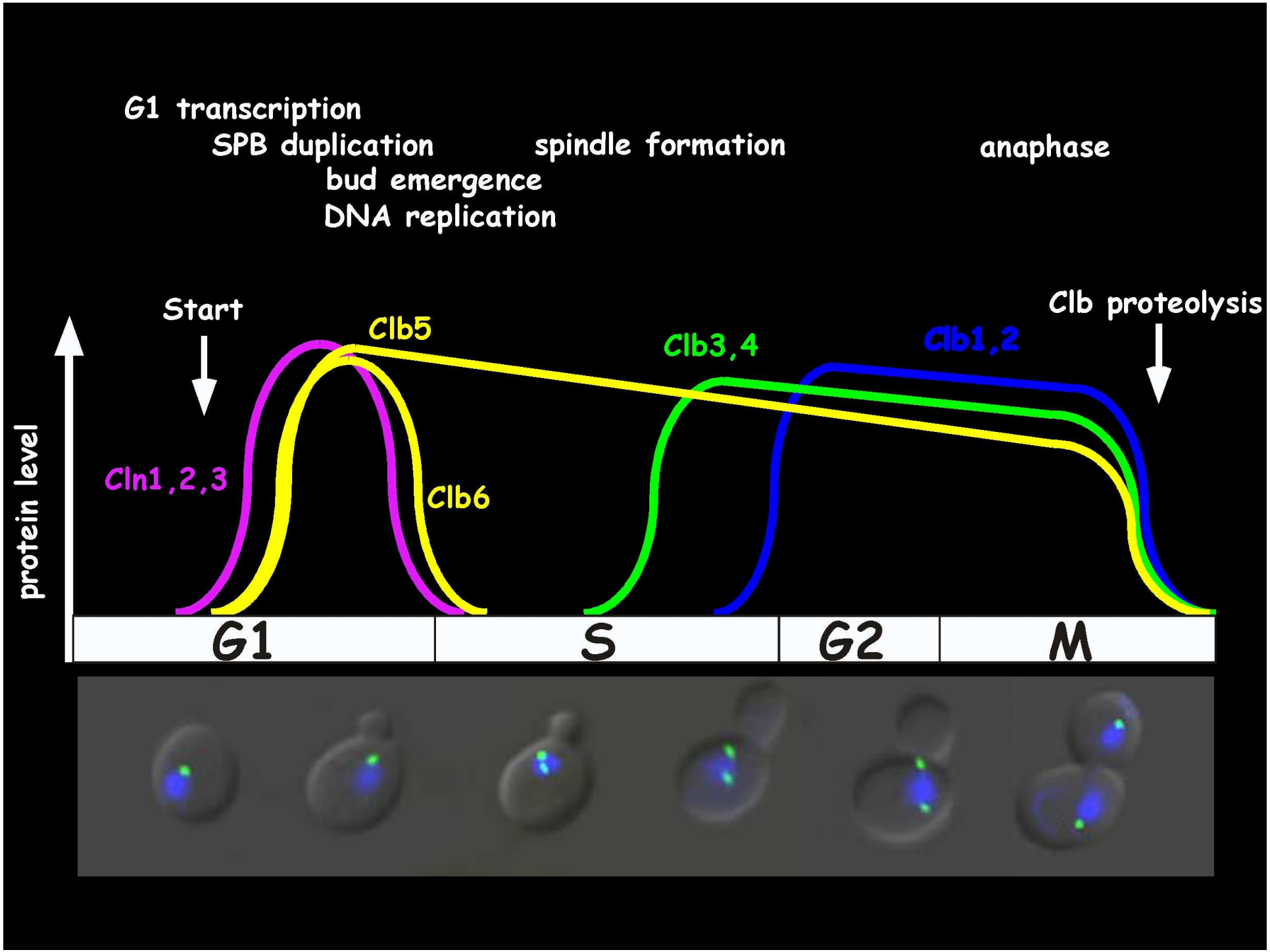
From The Cell Cycle: Principles of Control by David O Morgan



Somatic Cell Cycles

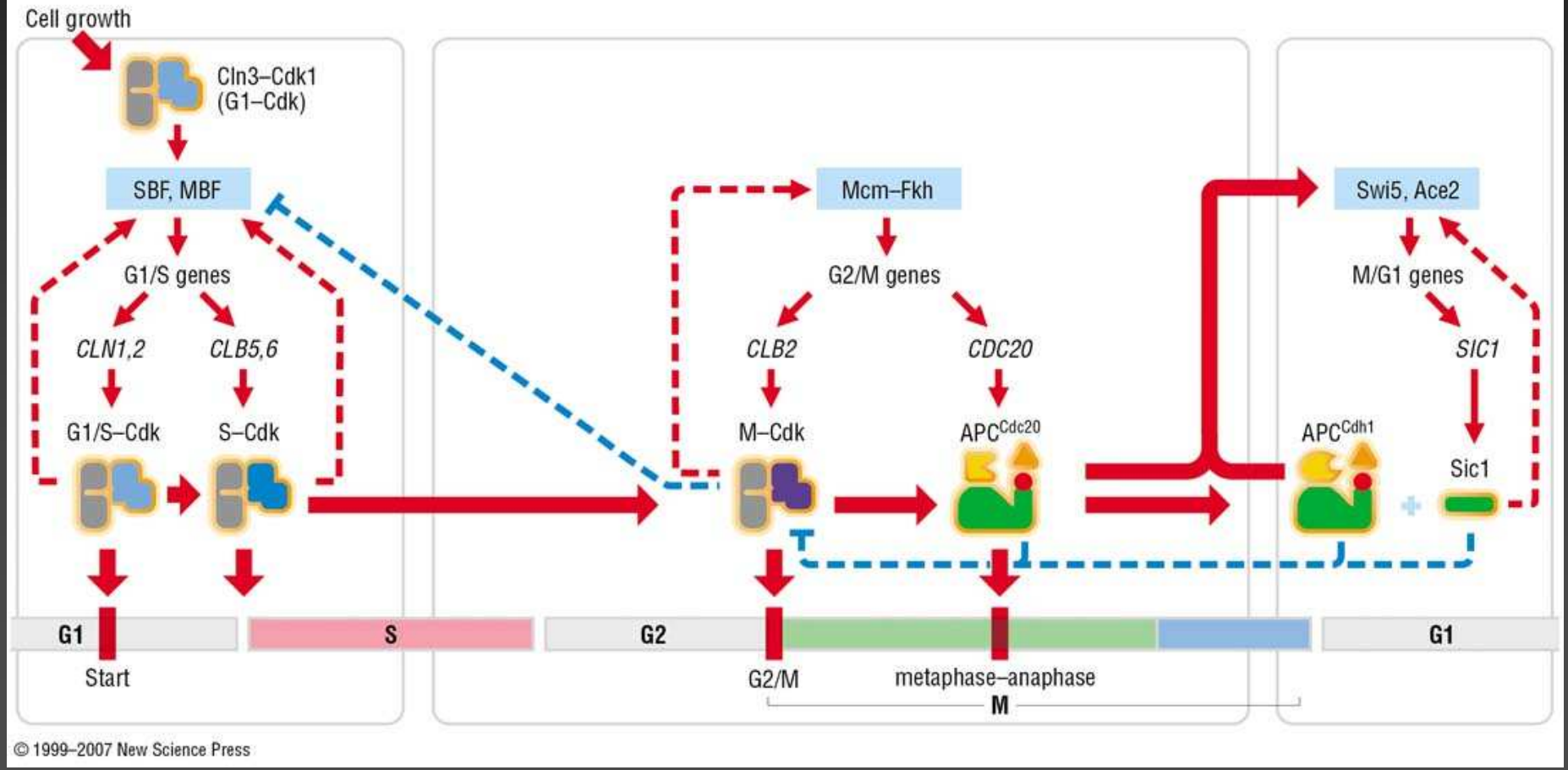
- extended cell-cycle period
- multiple cyclin/CDKs

Budding yeast cell cycle

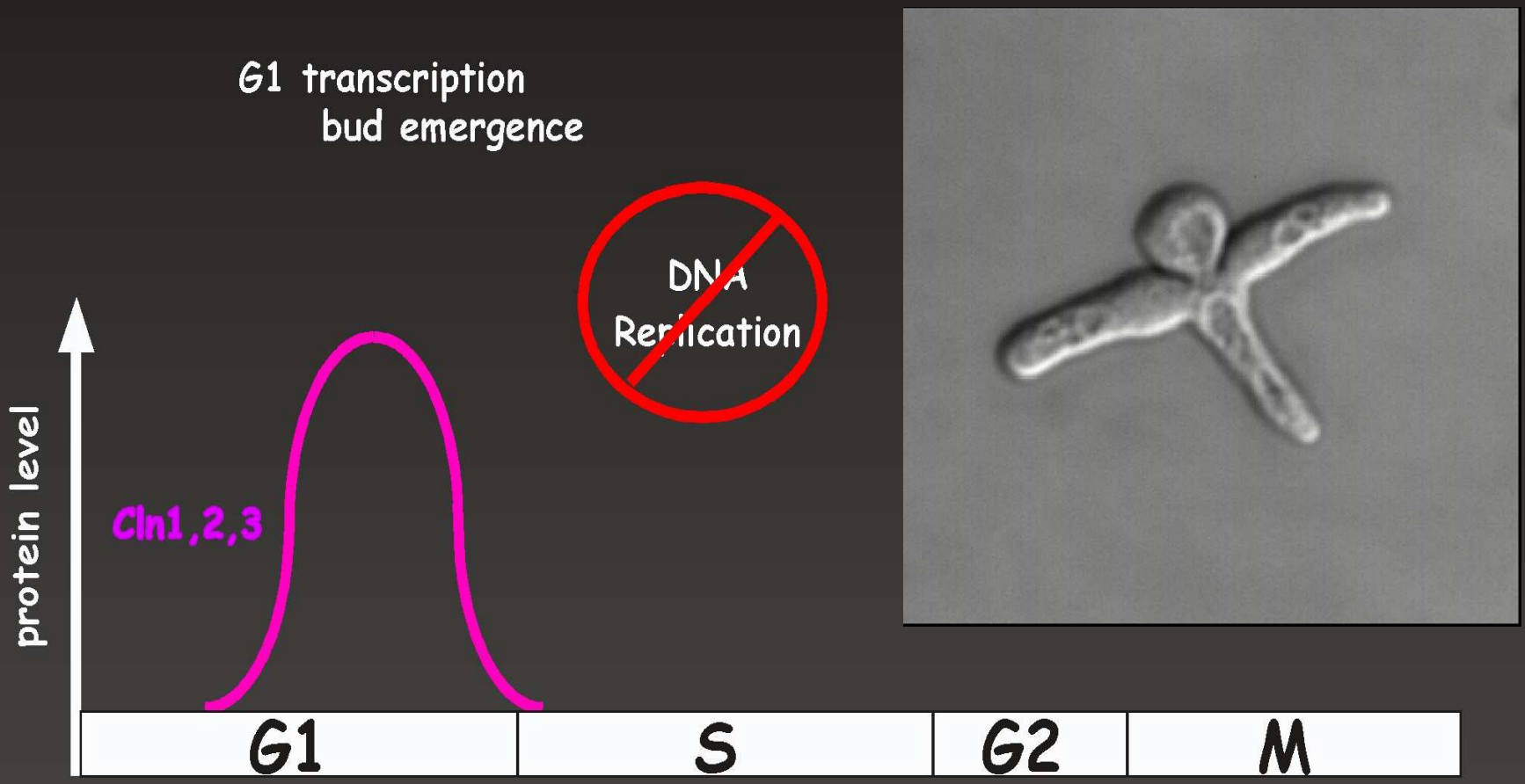

G1 transcription
SPB duplication
bud emergence
DNA replication
spindle formation
anaphase
Start
Clb proteolysis
Clb5
Clb3,4
Clb1,2
Cln1,2,3
Clb6
protein level
G1
S
G2
M

Budding Yeast

From **The Cell Cycle: Principles of Control** by David O Morgan

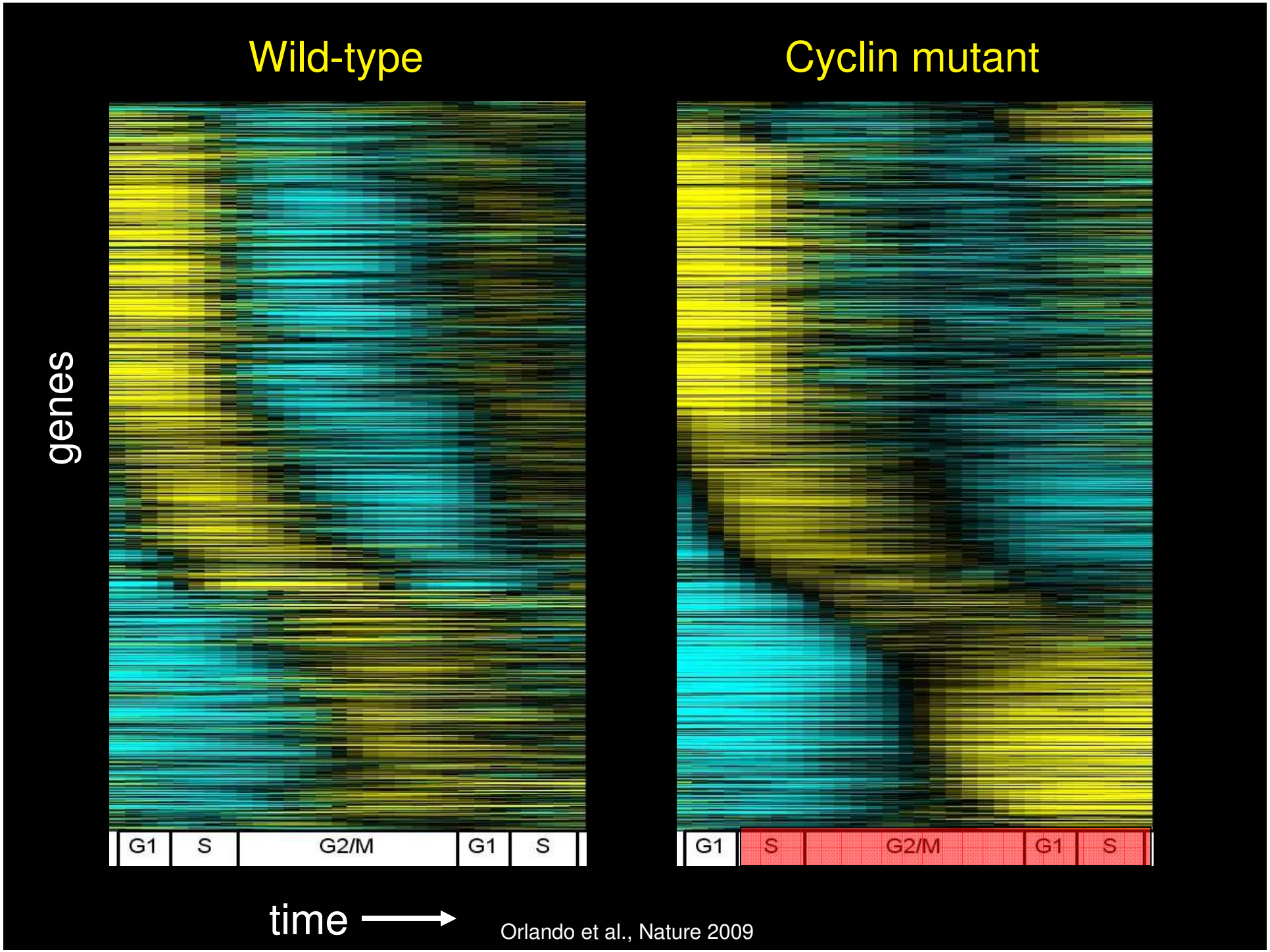


Δclb1,2,3,4,5,6 GAL-CLB1



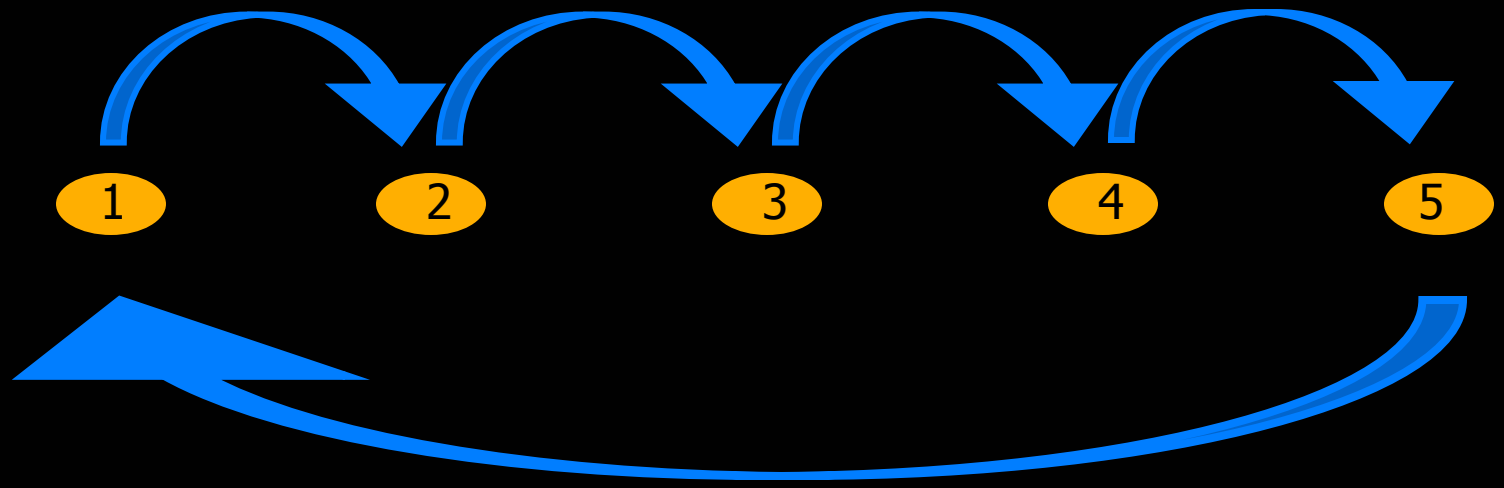
Examine global transcription dynamics

Haase and Reed, Nature 1999

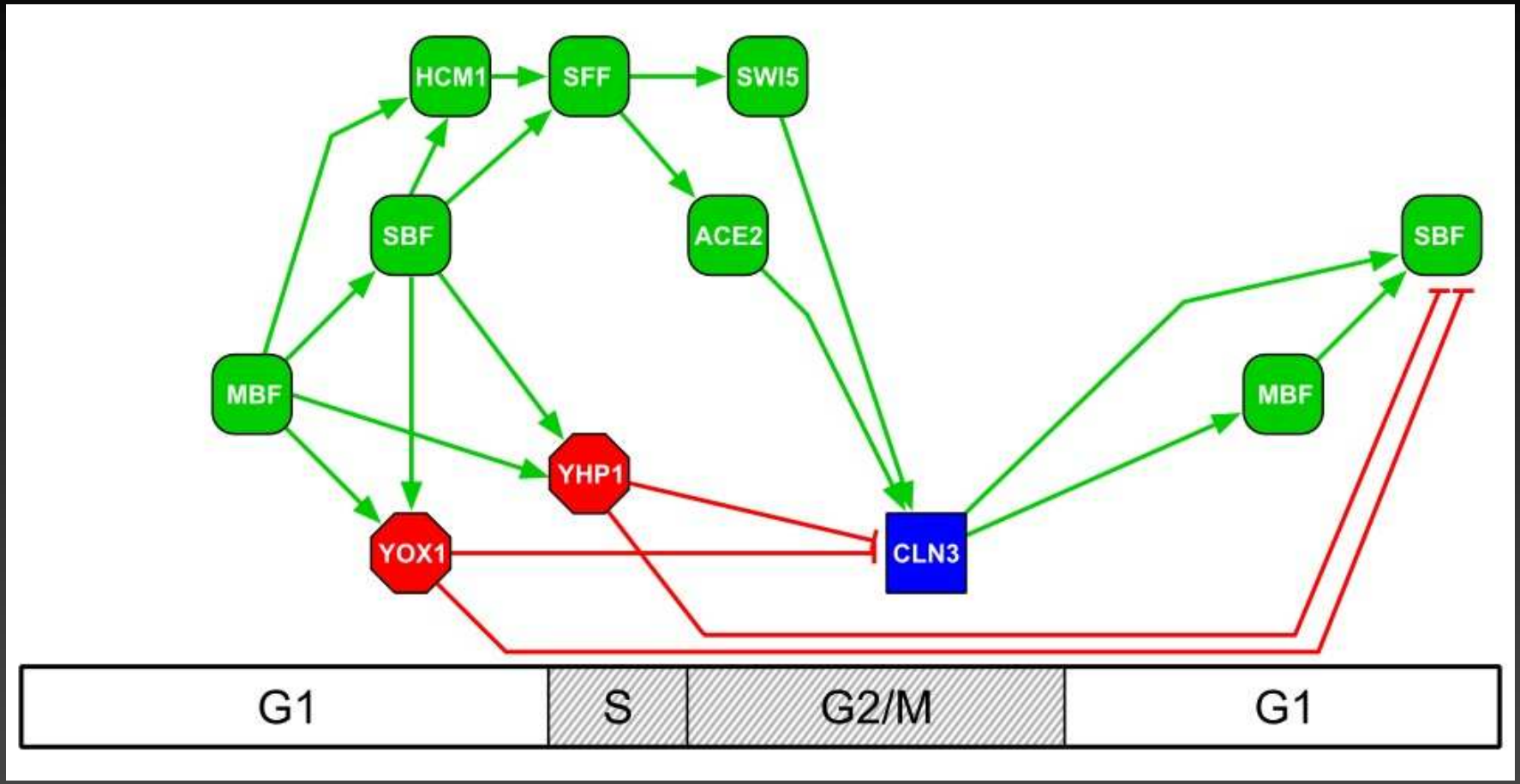


Orlando et al., Nature 2009

How is periodic transcription regulated in cyclin mutants?



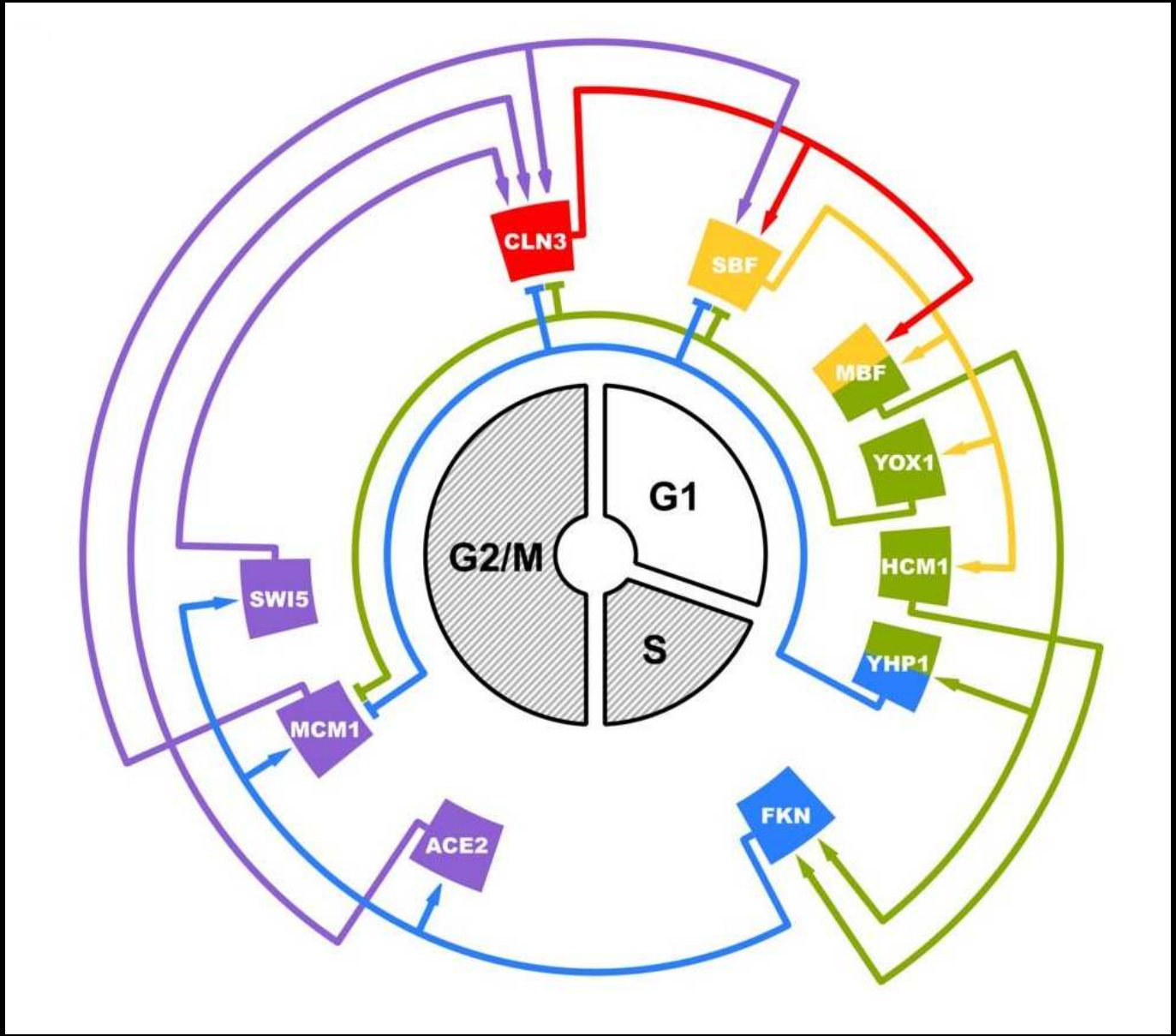
Could a TF network function as an oscillator independent of cyclin/CDKs?

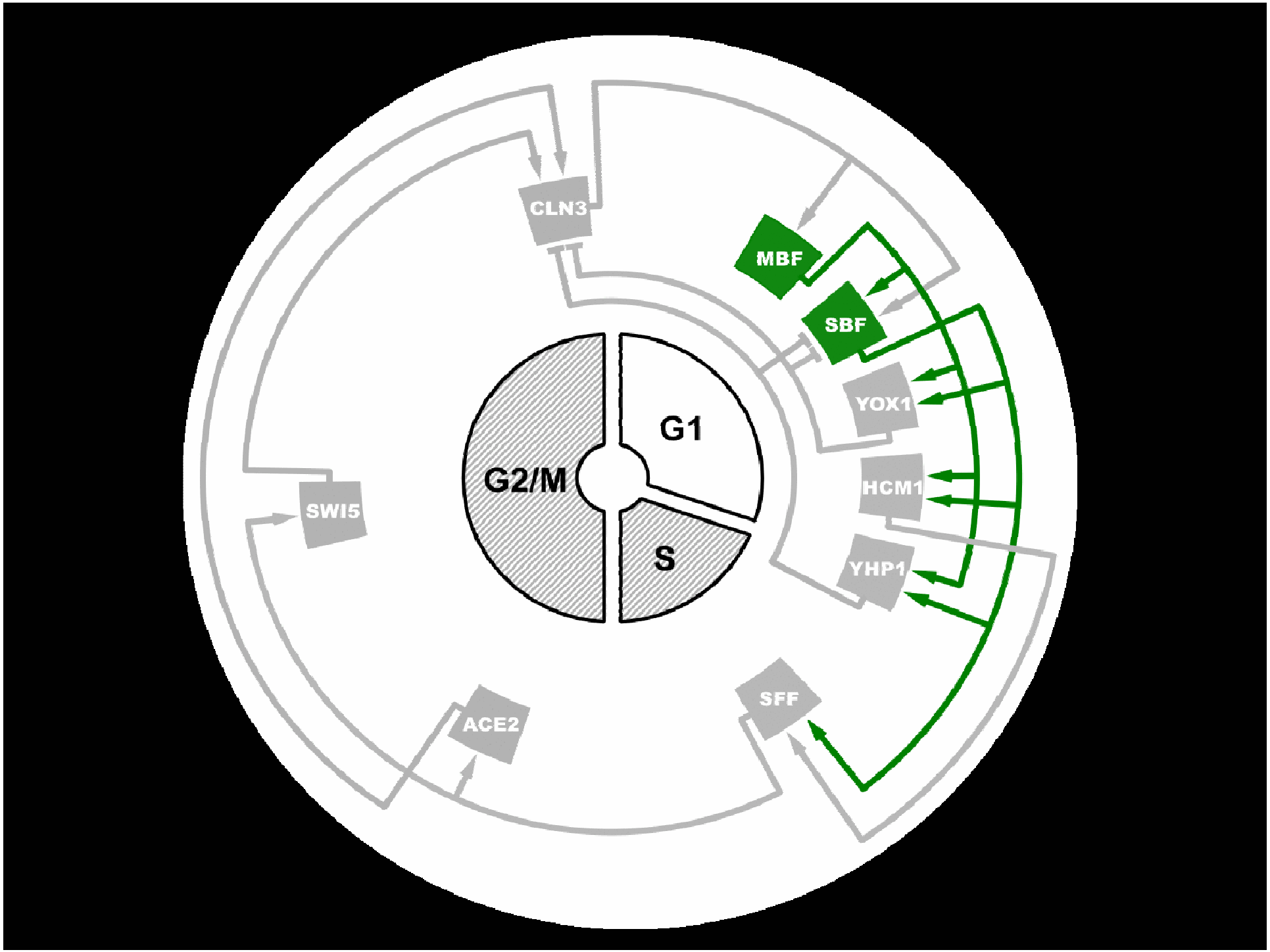


- Nodes: TFs that maintain periodic transcription in cyclin mutants

- Edges: high confidence TF/promoter interactions $p < .001$

A synchronously updating Boolean model

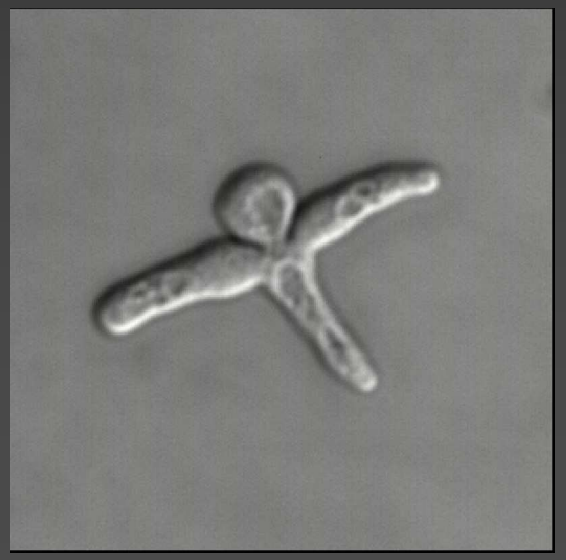



CLN3
MBF
SBF
YOX1
HCM1
YHP1
SFF
ACE2
SWI5
G1
S
G2/M

A transcription network oscillator model

- functions independent of S-phase and mitotic CDKs
- independent of cell-cycle progression
- temporal transcription program
- robust oscillations with similar period

(Socolar and Harer groups: autonomous Boolean models)



Outstanding questions:

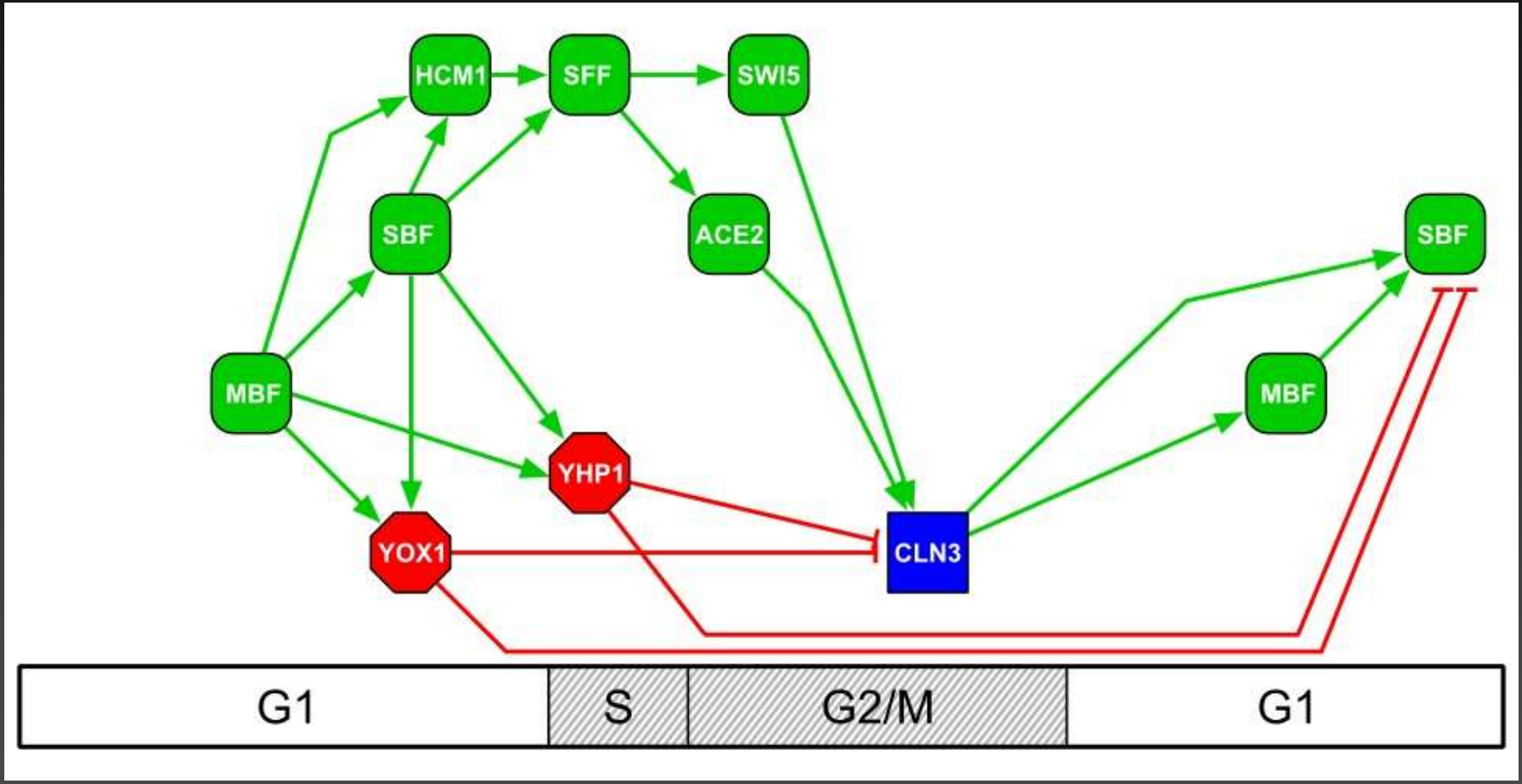
1. Can the network oscillator function independent of all cyclin/CDKs ?

2. What happens to network oscillator function during a checkpoint arrest ?

3. Transcription network oscillator in bigger eukaryotes ?

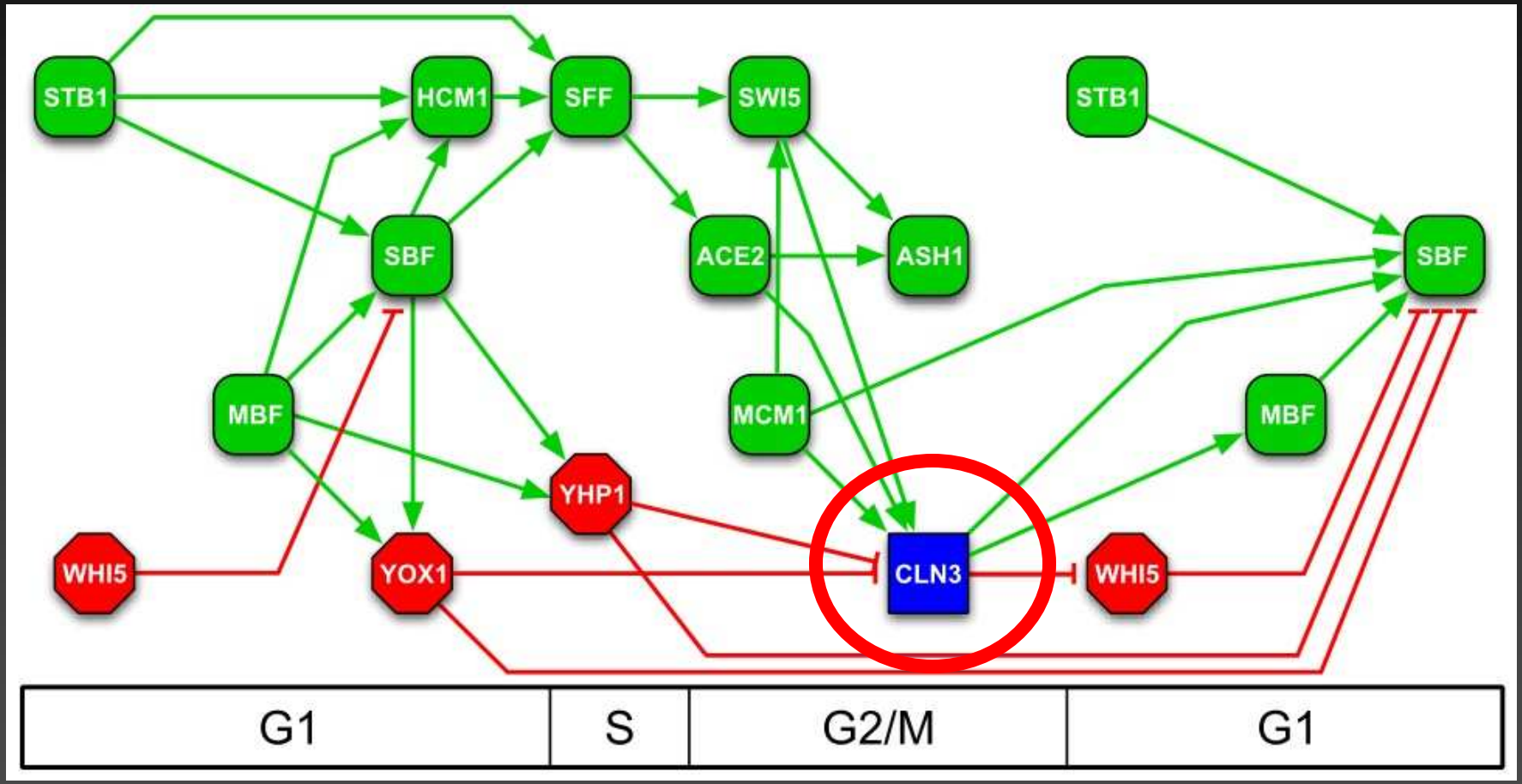
What's wrong with this network model?

this network is more complex…



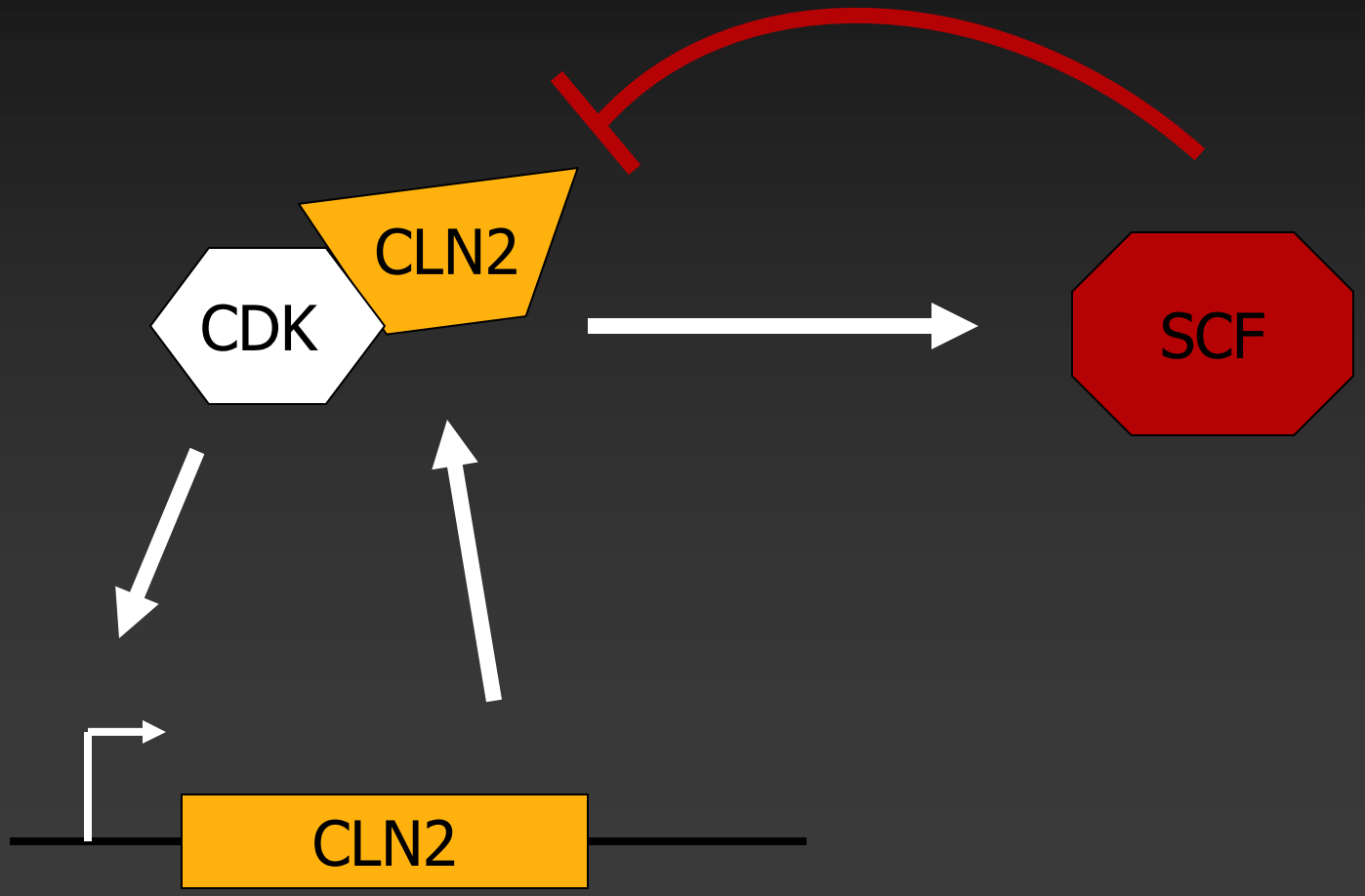
- nodes were pruned if they had no inputs or outputs. Edges ($p < .001$)

Does network function require G1 cyclins?



- Goal: identify complete network

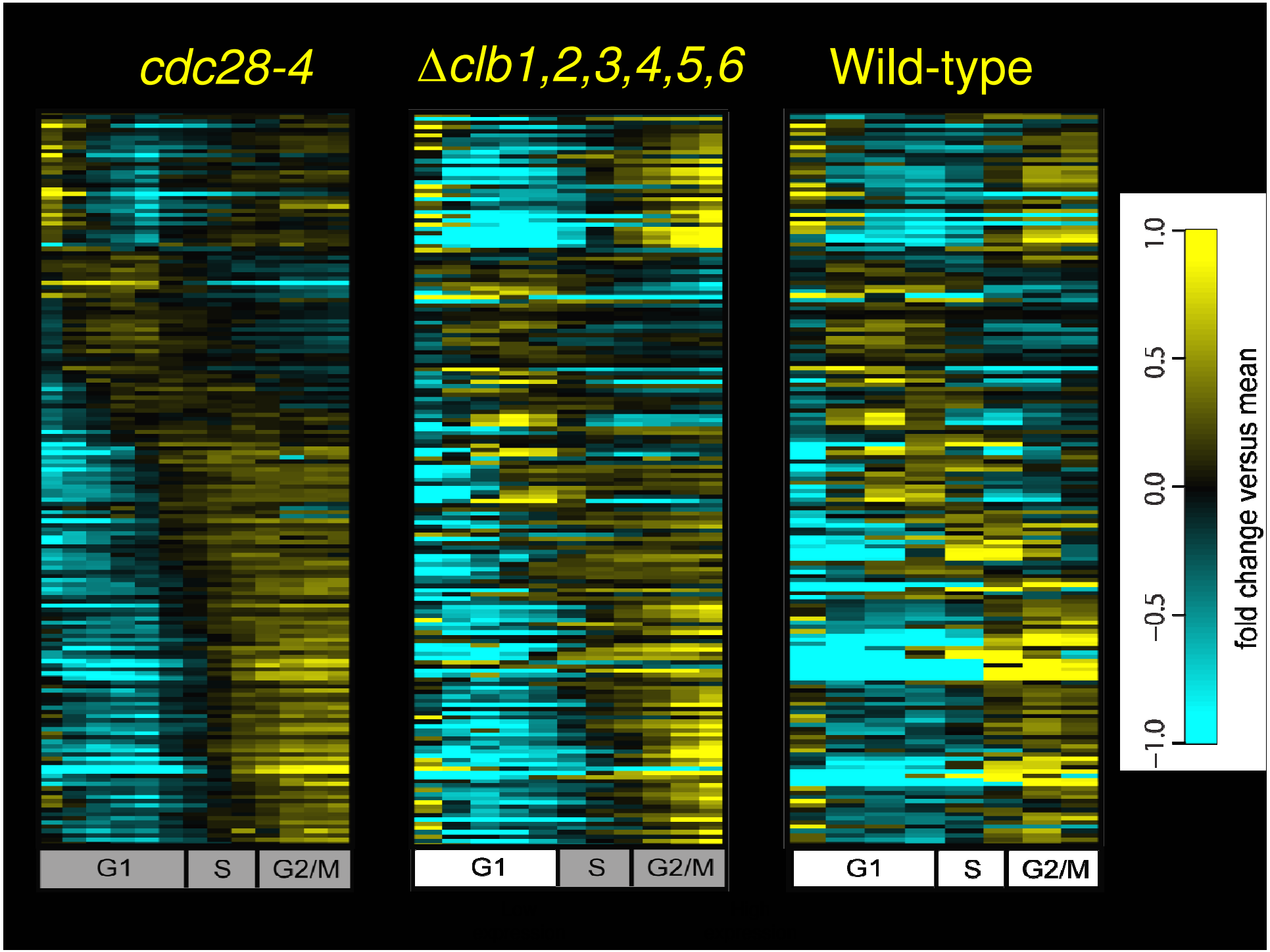
Can G1 cyclins function as an oscillator?



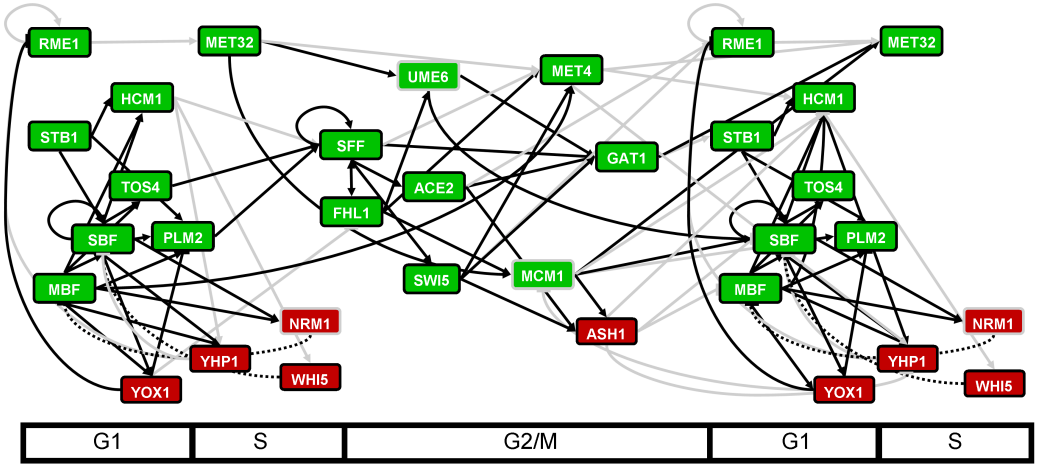
Transcriptional profiling in cells lacking all cyclin/CDK activities

- Temperature sensitive mutation of Cdk1 *(cdc28-4)*

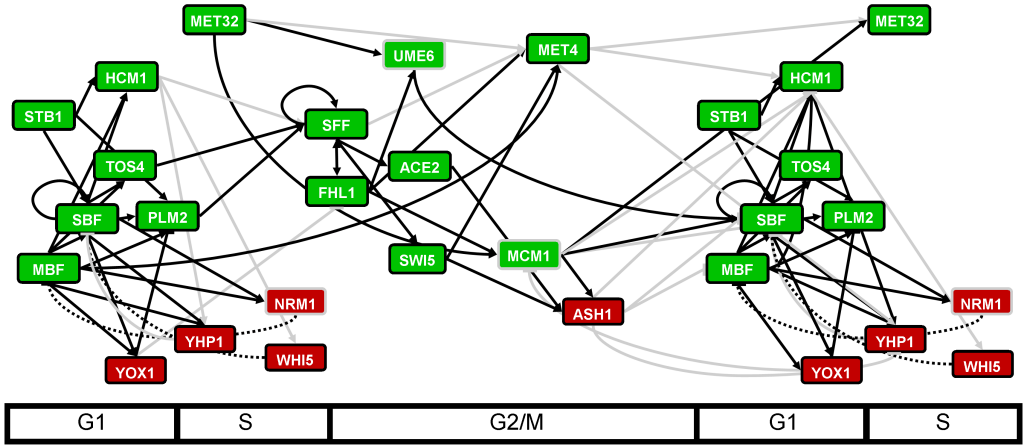
-*cdc28-4* mutant cells arrest in G1 (no apparent periodic activities)


cdc28-4
Δclb1,2,3,4,5,6
Wild-type
G1
S
G2/M
G1
S
G2/M
G1
S
G2/M
1.0
0.5
0.0
−0.5
−1.0
fold change versus mean

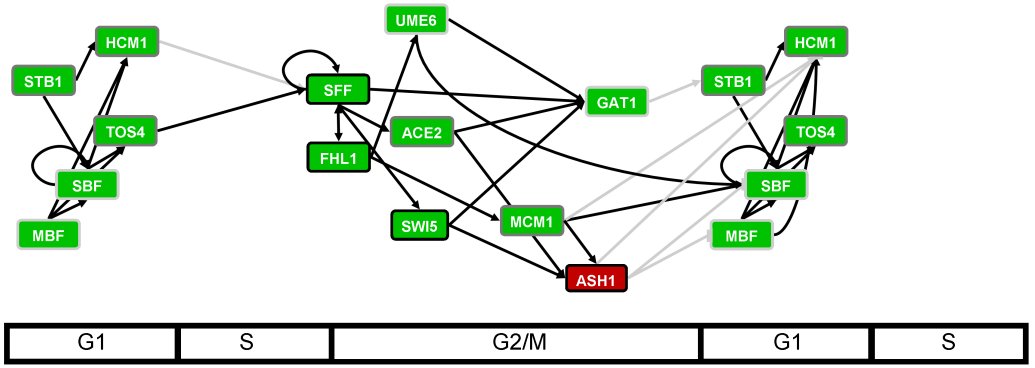
Wild-type



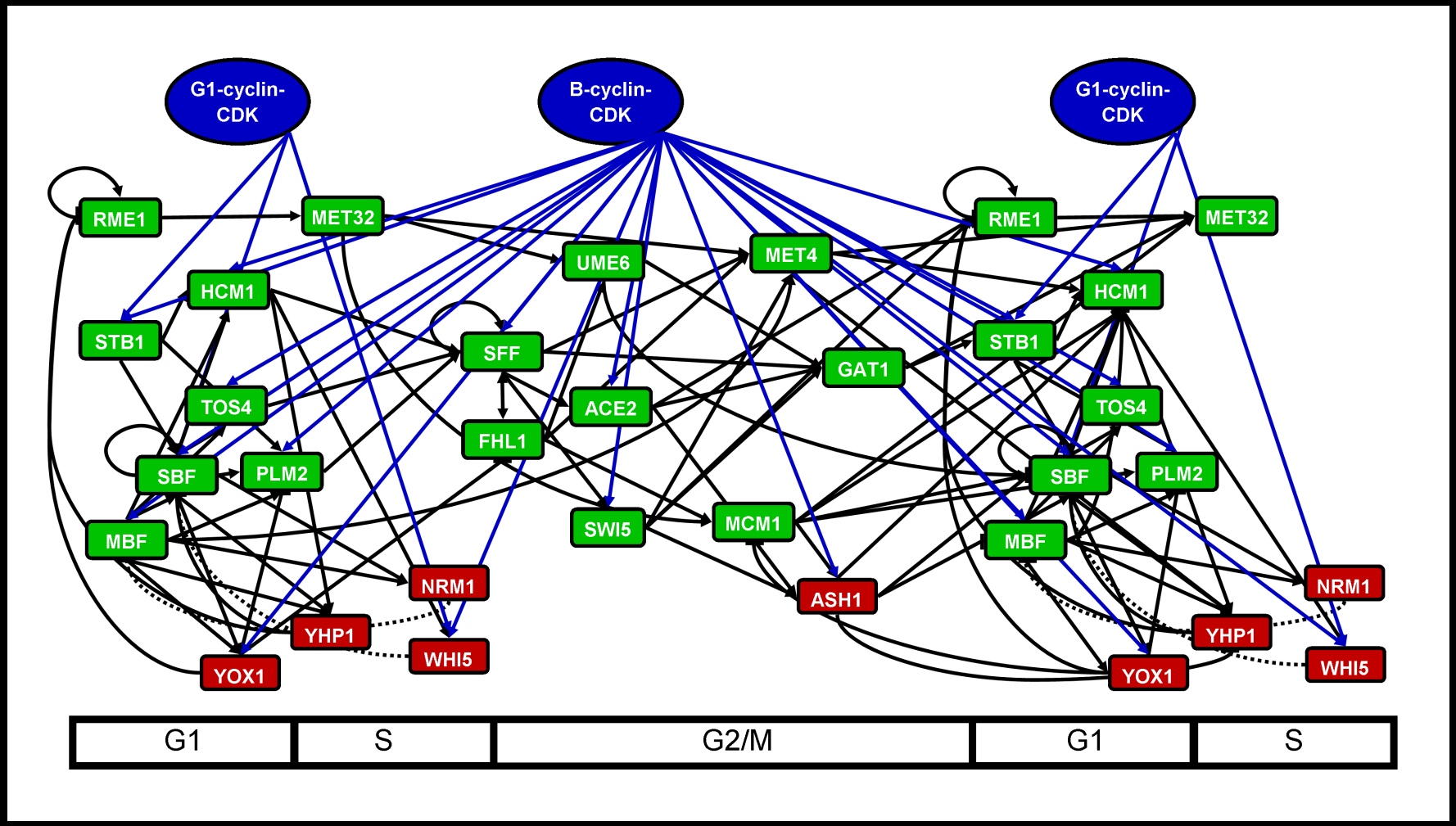
Δclb1,2,3,4,5,6



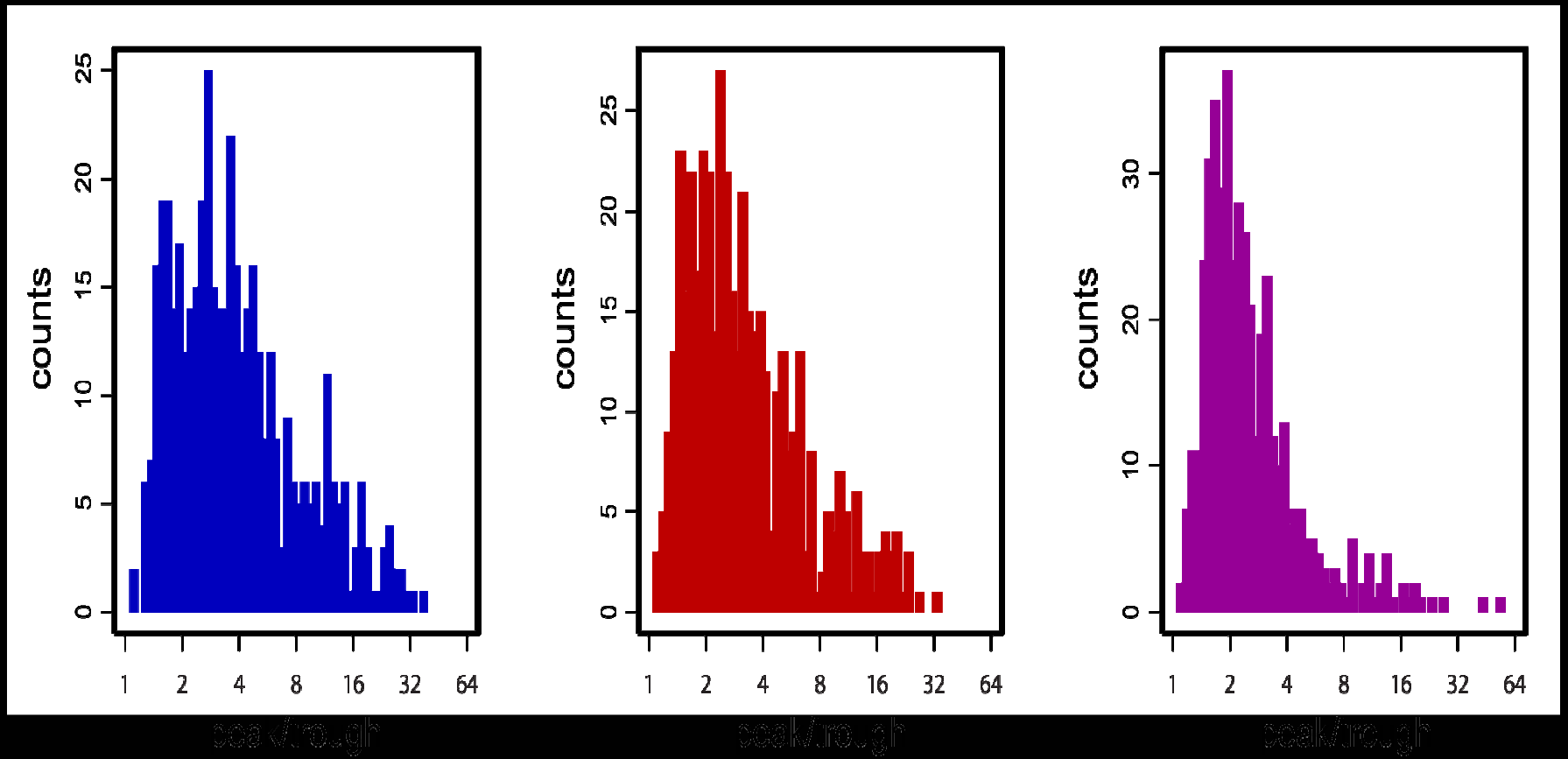
cdc28-4



A role for CDKs in regulating transcriptional oscillations?



Amplitude is lost when cyclin/CDK activities are reduced

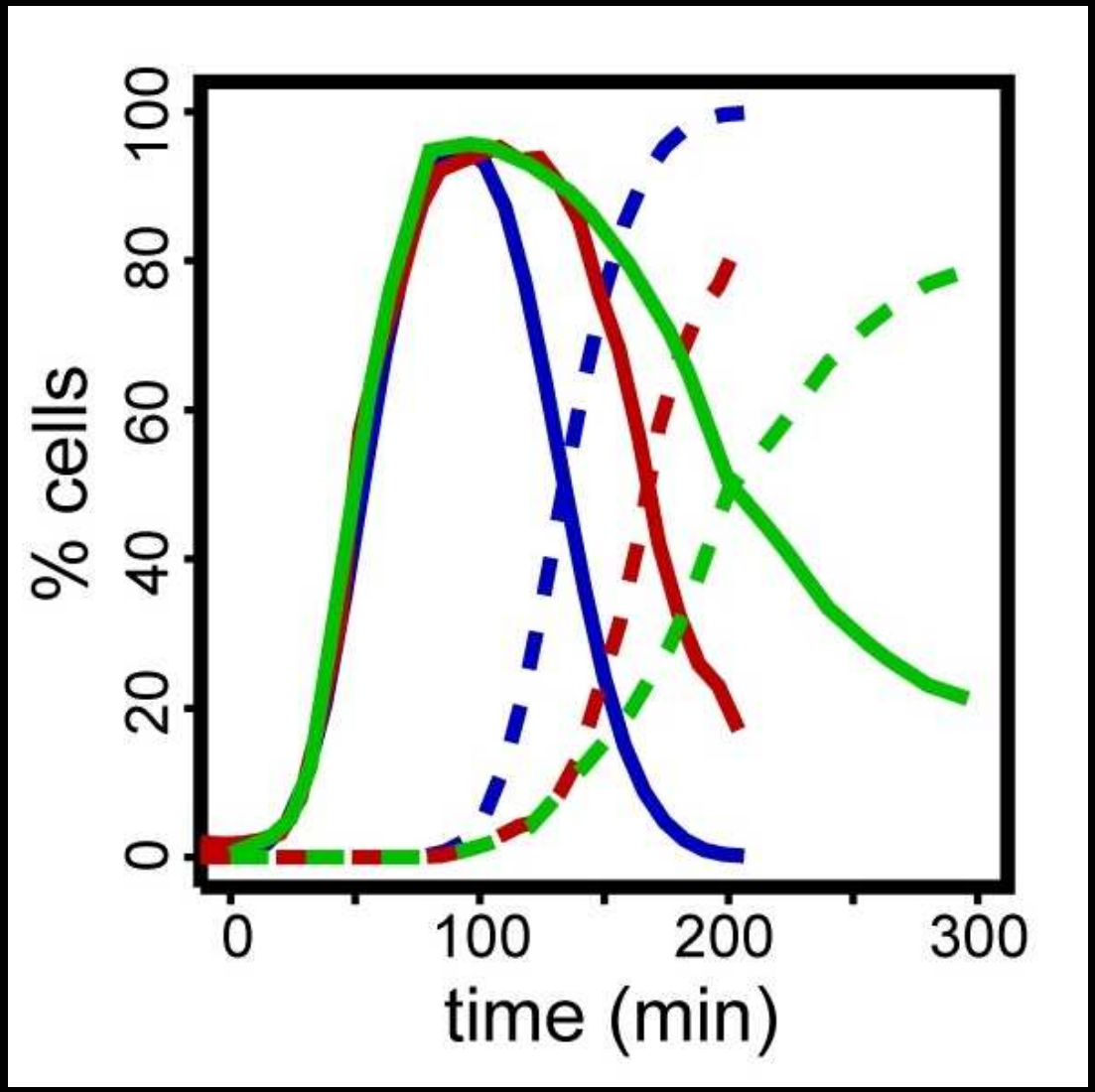


Wild-type

Δclb1,2,3,4,5,6

cdc28-4

Damped oscillations in cells lacking cyclin/CDK activities?



Wild-type

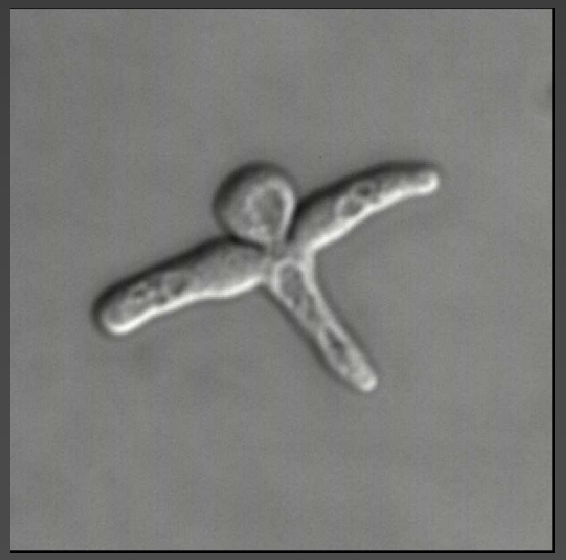
(-) B-cyclin/CDK

(-) all cyclin/CDK

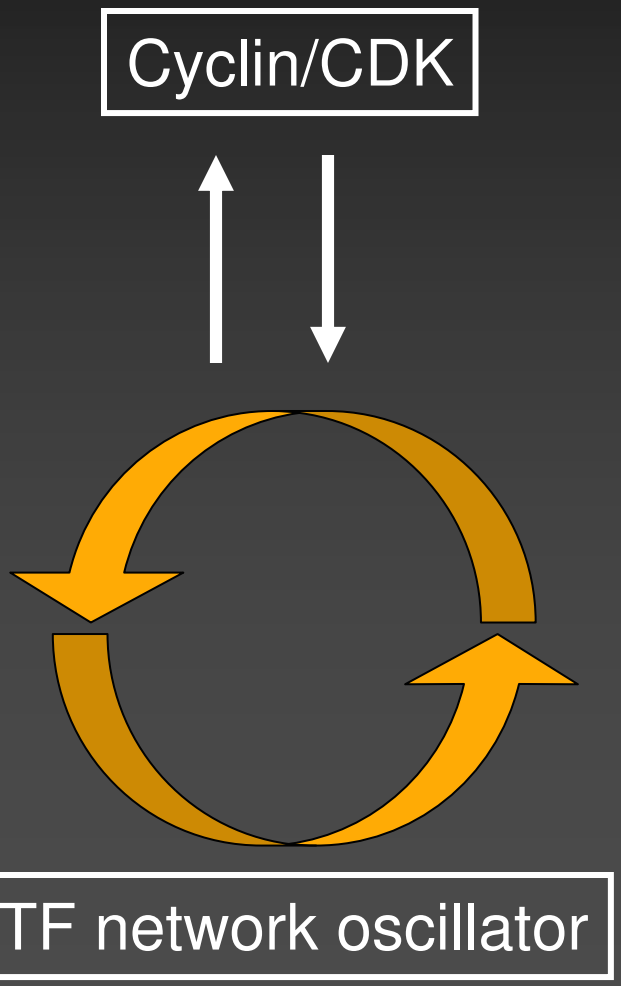
- network oscillator can function independent of all cyclin/CDKs

- cyclin/CDKs contribute to robust cell cycle oscillations

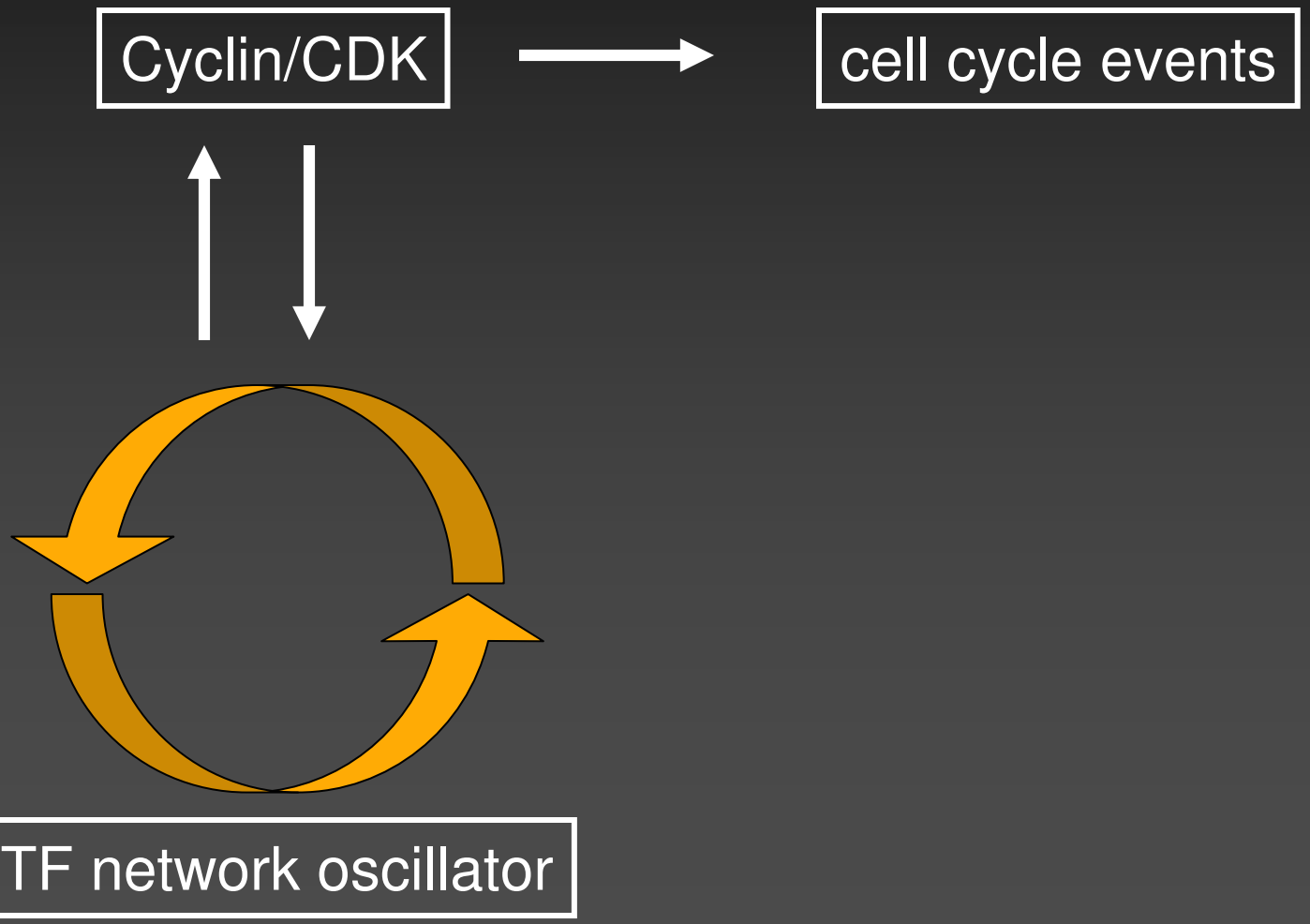
- cyclin/CDKs act as effectors of the oscillator



yeast cells (somatic cells)

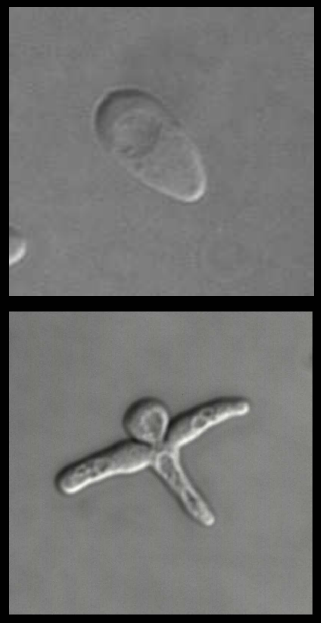


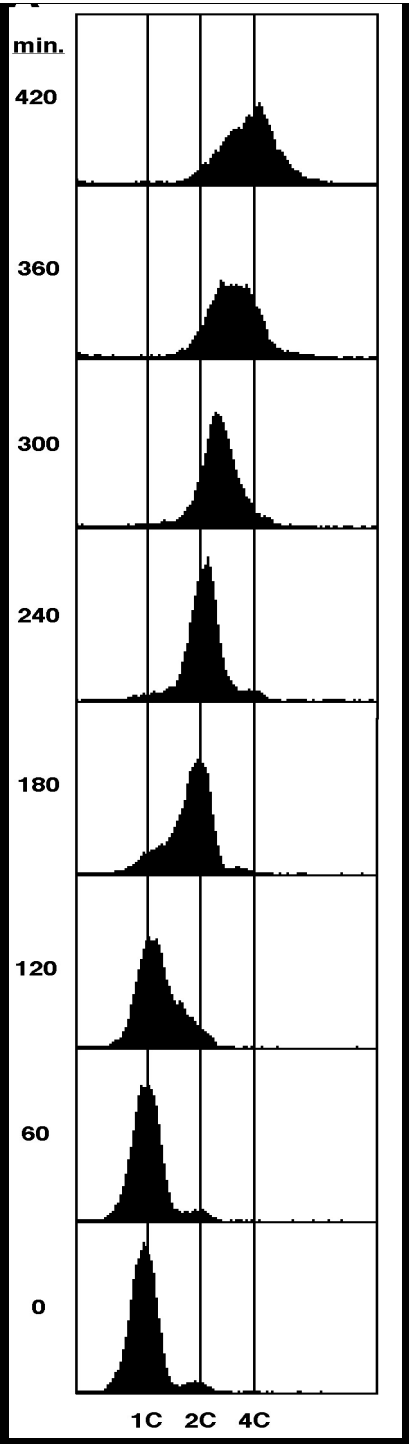
Somatic cells and yeast cells



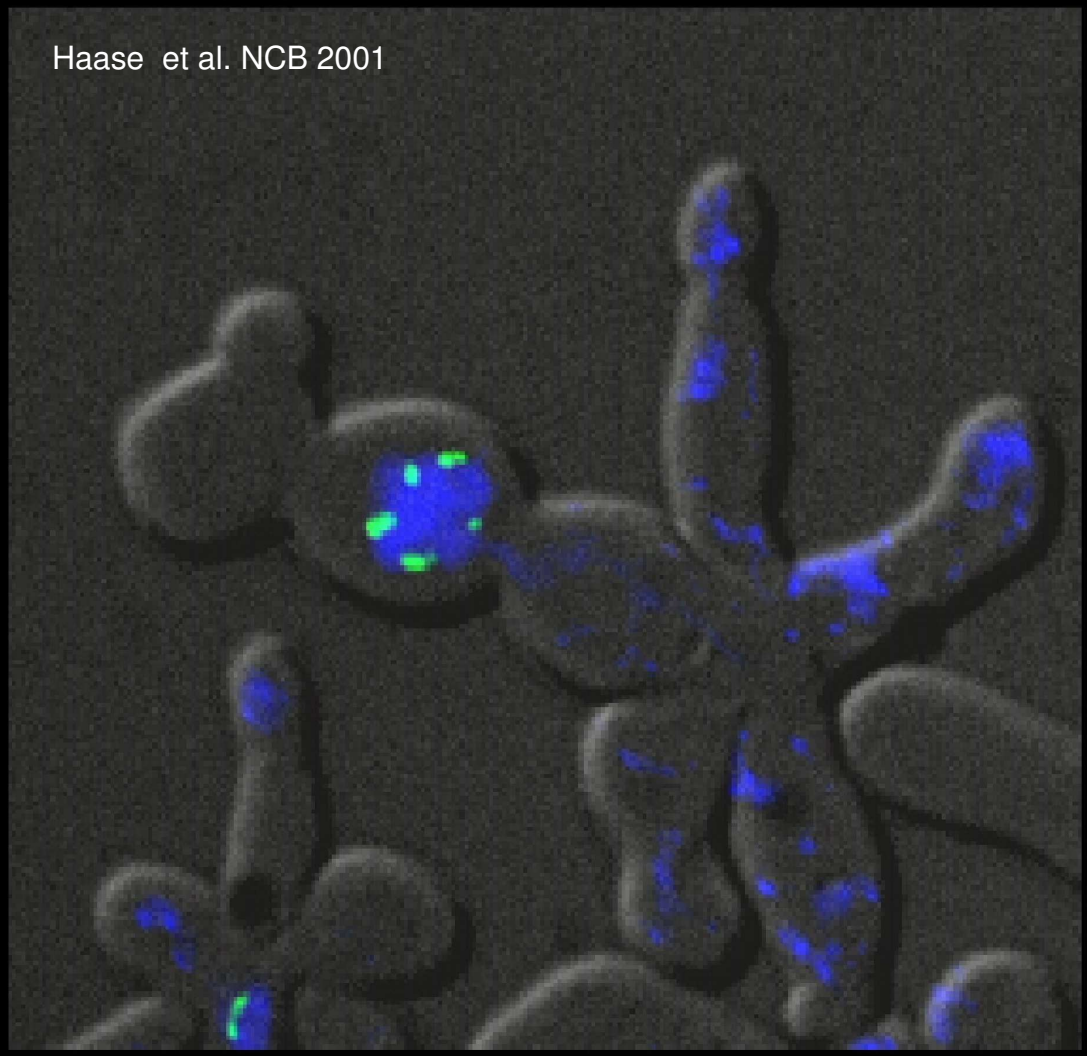
CDKs as effectors of TX network oscillator?

- periodic events should be determined by the cyclins expressed…

CDKs present	cyclic behaviors
none (*cdc28-4*)	
G1-CDKs *(Δclb1,2,3,4,5,6)*	
G1- and S-CDKs *(Δclb1,2,3,4,5)*	?



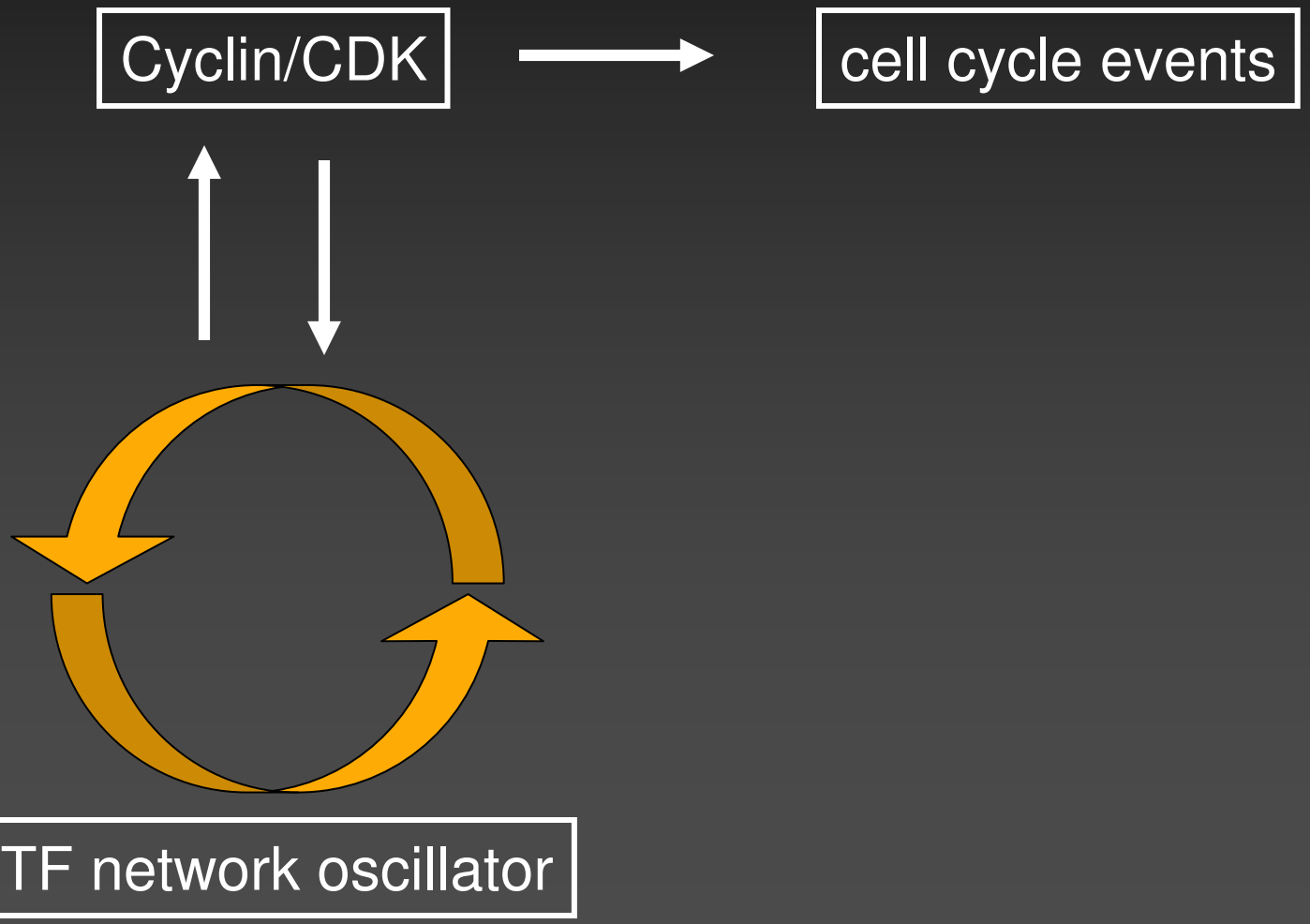
G1- and S-CDKs
(Δ*clb1,2,3,4,5 CLB6*)
Clb6 = cyclin E



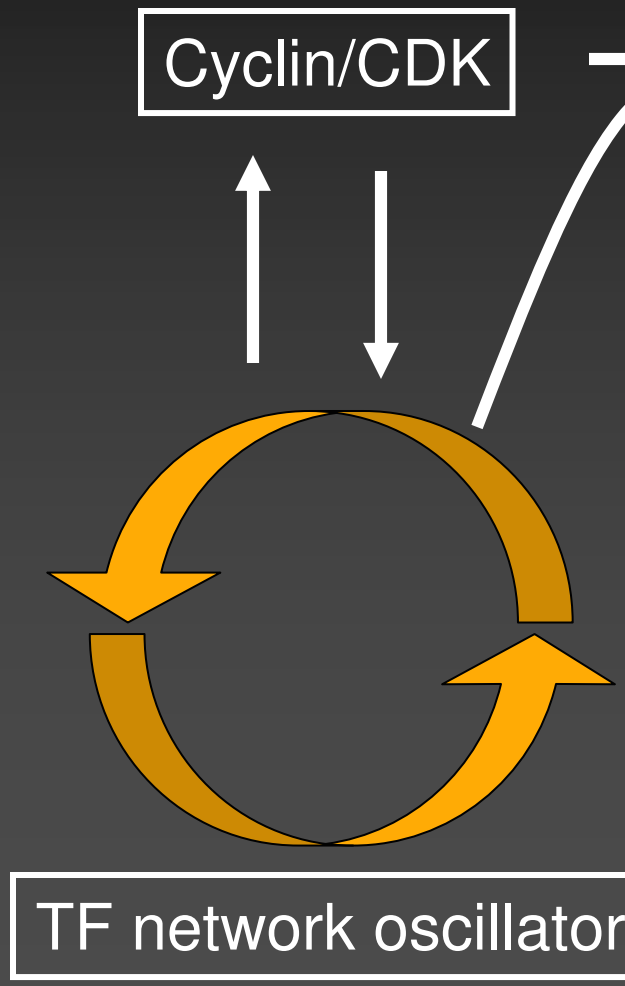
CDKs as effectors of transcriptional oscillator?

CDKs present	cyclic behaviors
none (*cdc28-4*)	none
G1-CDKs *(Δclb1,2,3,4,5,6)*	budding
G1- and S-CDKs *(Δclb1,2,3,4,5)*	budding, DNA replication, SPB duplication

Somatic cells and yeast cells



Somatic cells and yeast cells



"Just in time transcription"

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