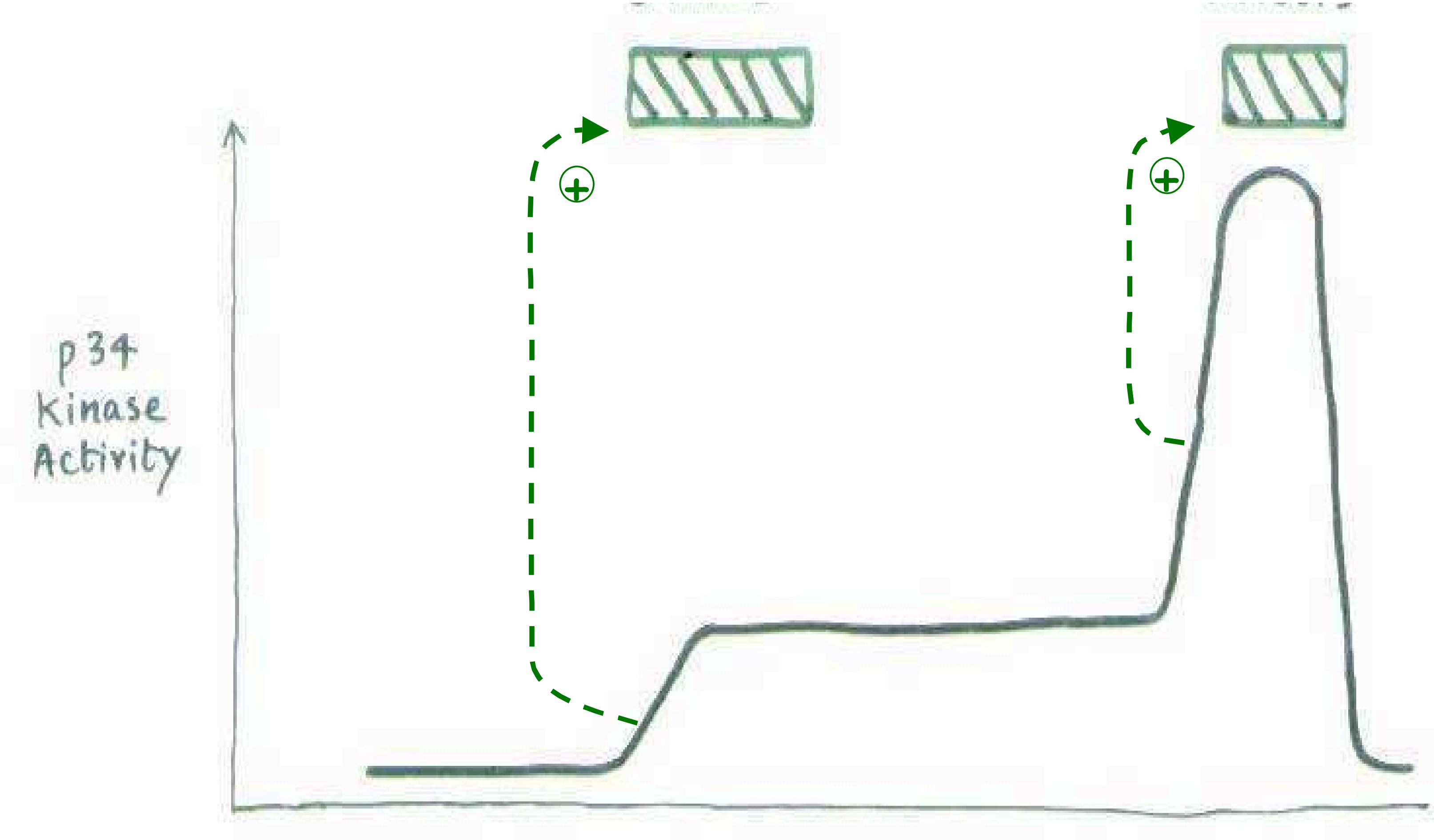
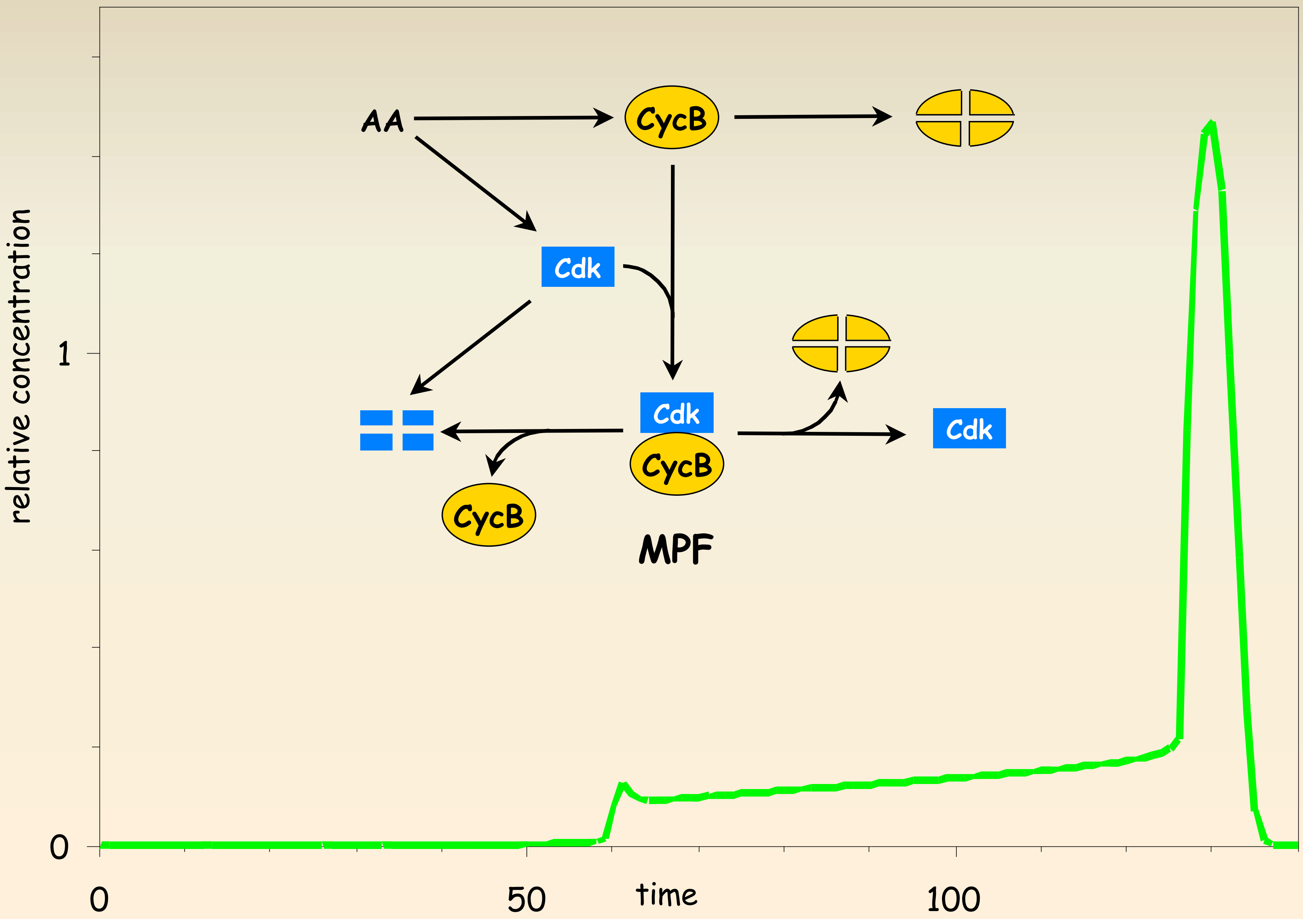
CYCLIN DEPENDENT KINASES AND CELL CYCLE CONTROL

Nobel Lecture, December 9, 2001

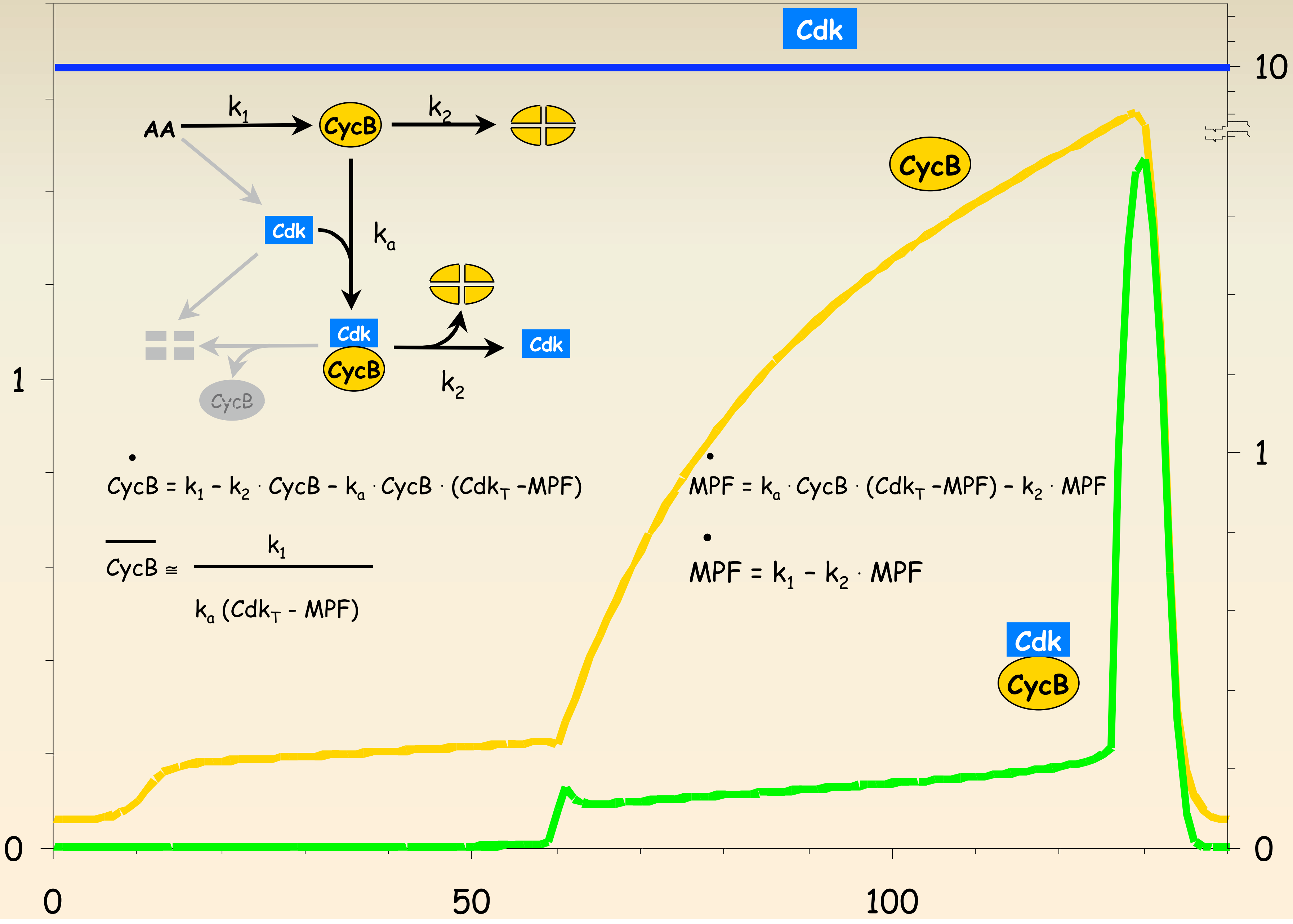
by

PAUL M. NURSE

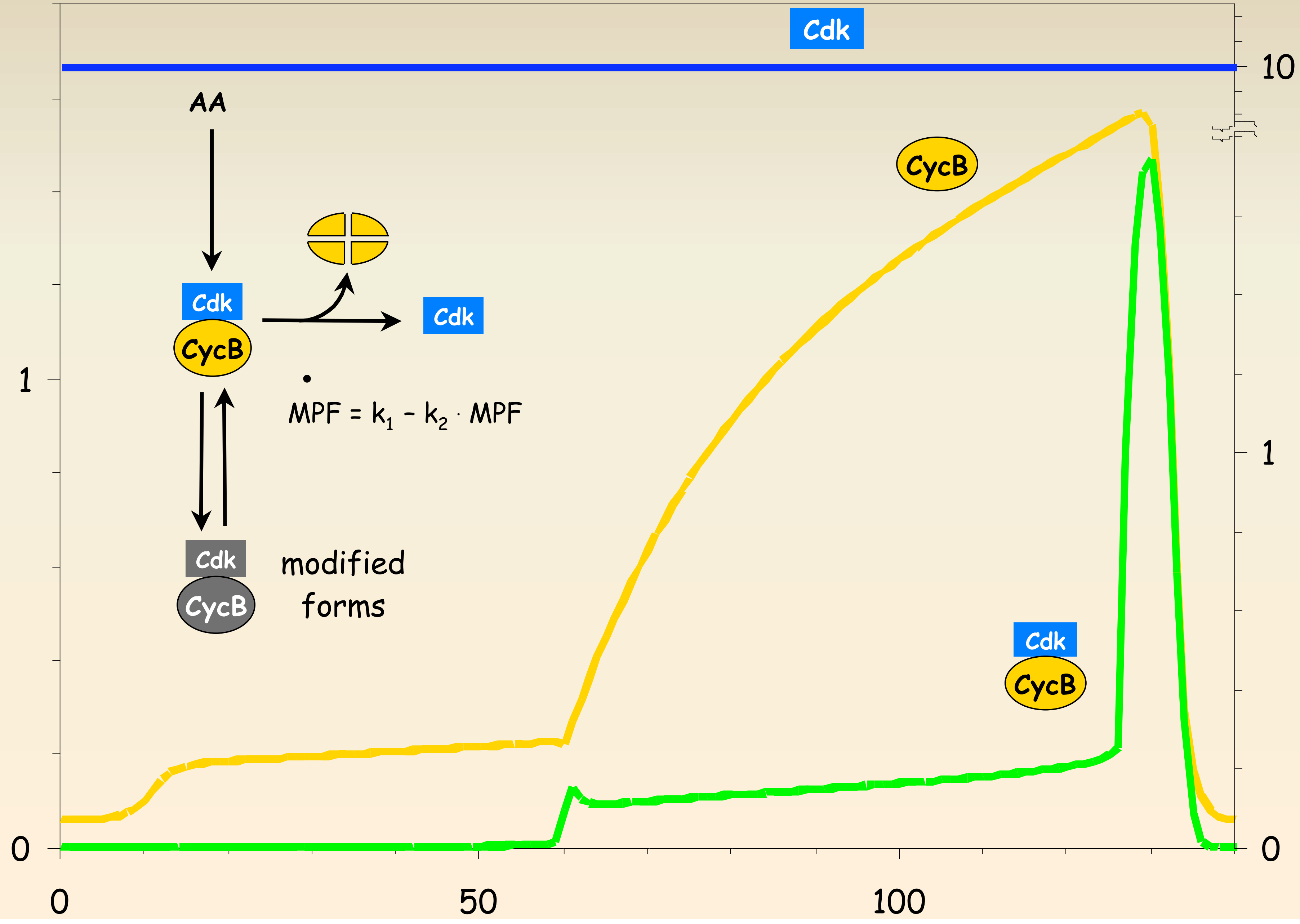



AA
CycB
Cdk
Cdk
CycB
CycB
Cdk
MPF
relative concentration
1
0
0
50
time
100

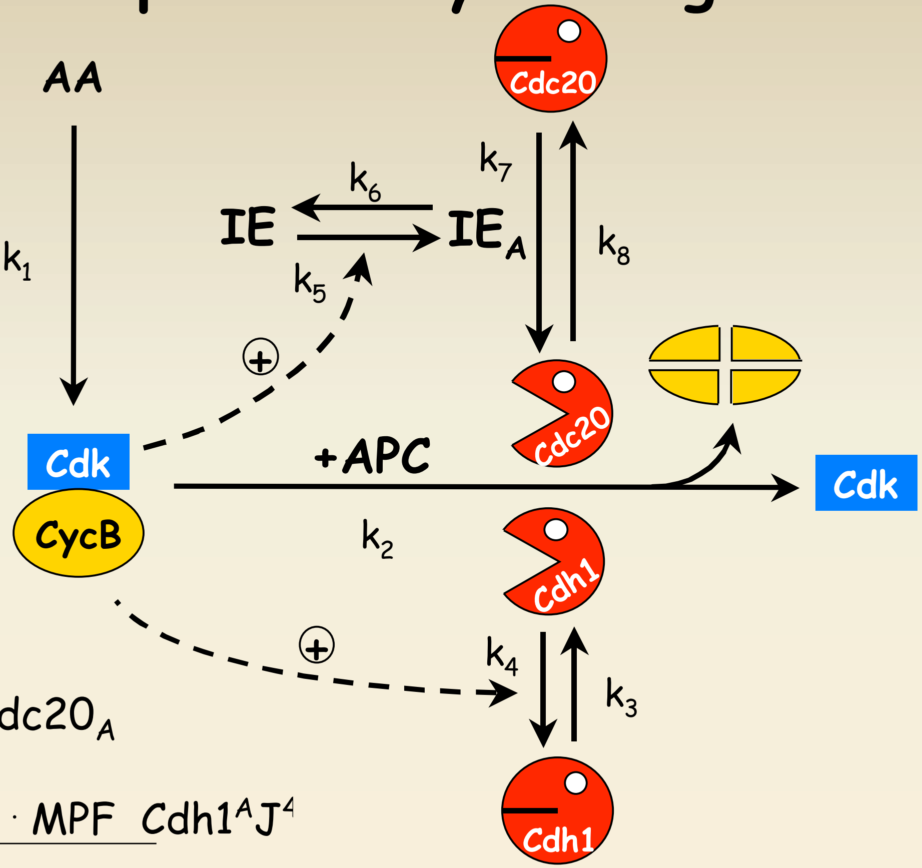
Cdk level is constant & CycB level is fluctuating



Cdk level is constant & CycB level is fluctuating



Two classes of proteins promote cyclin degradation

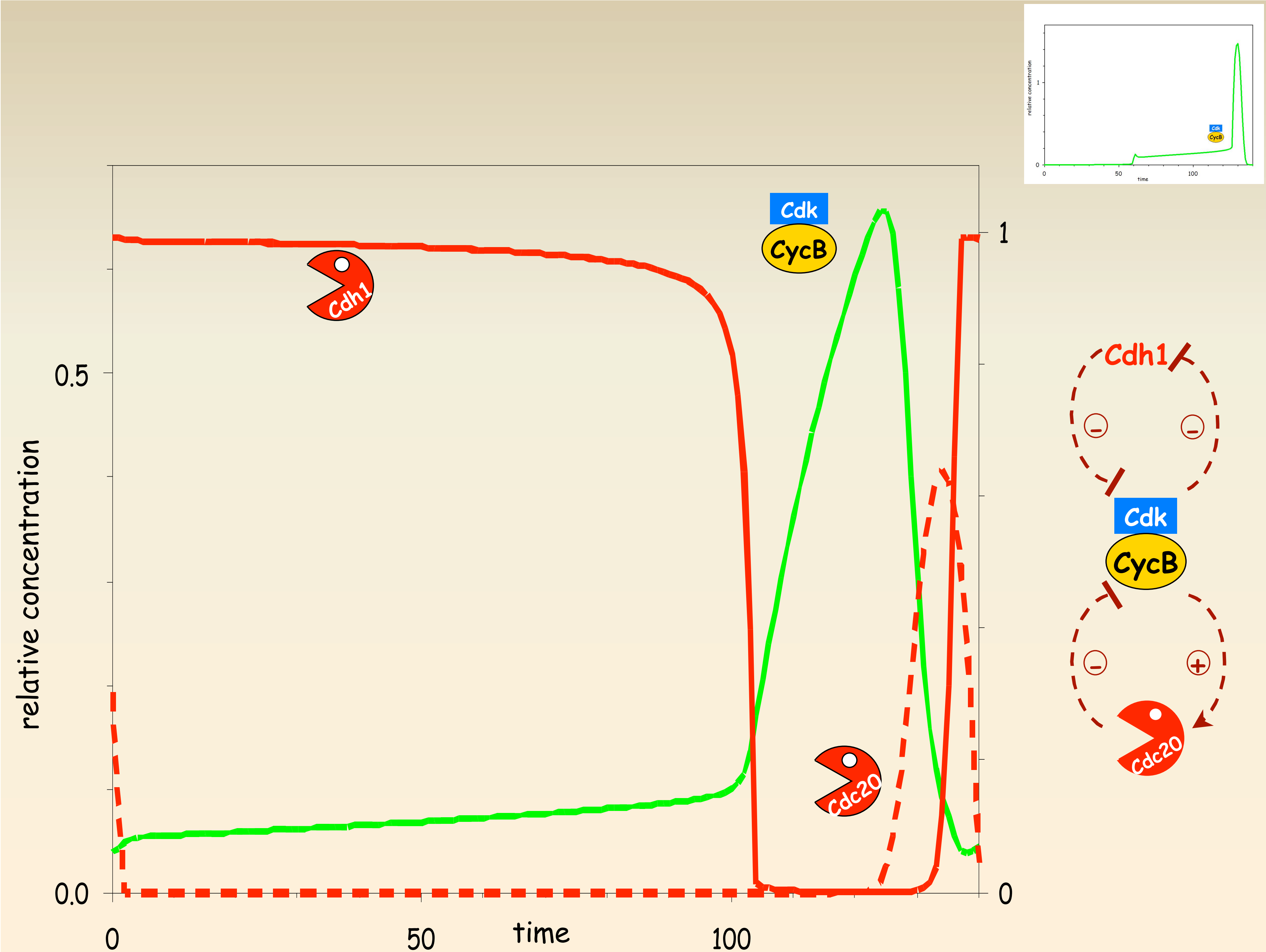


$$\dot{MPF} = k_1 - k_2 \cdot MPF$$

where $k_2 = k_2' + k_2'' \cdot Cdh1_A + k_2''' \cdot Cdc20_A$

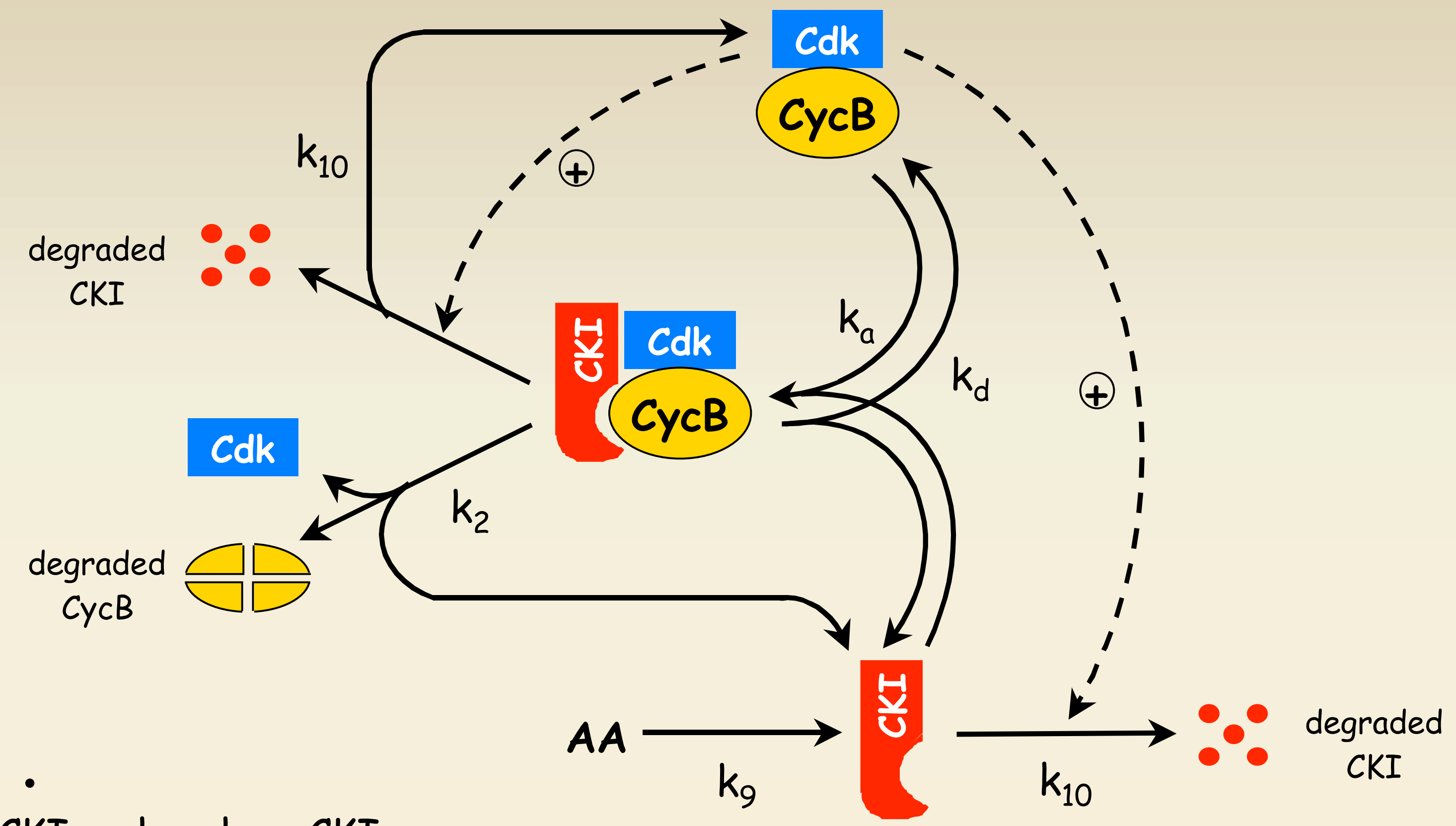
$$\dot{Cdh1}^A = k^3 \, \underline{1 - Cdh1^A J^3 +} \, 1 - Cdh1^A - \underline{k^4 \cdot MPF} \, Cdh1^A J^4$$

$$\dot{IE}^A = k^5 \cdot MPF \, \underline{1 - IE^A J^5 +} \, 1 - IE^A \, \underline{- k^6 \cdot} \, IE^A J^6 + IE^A Cdc20^A$$



Cdk
CycB
Cdh1
Cdc20
relative concentration
time
0.5
0.0
0
50
100
1
0
Cdh1
Cdk
CycB
Cdc20

Adding a stoichiometric inhibitor



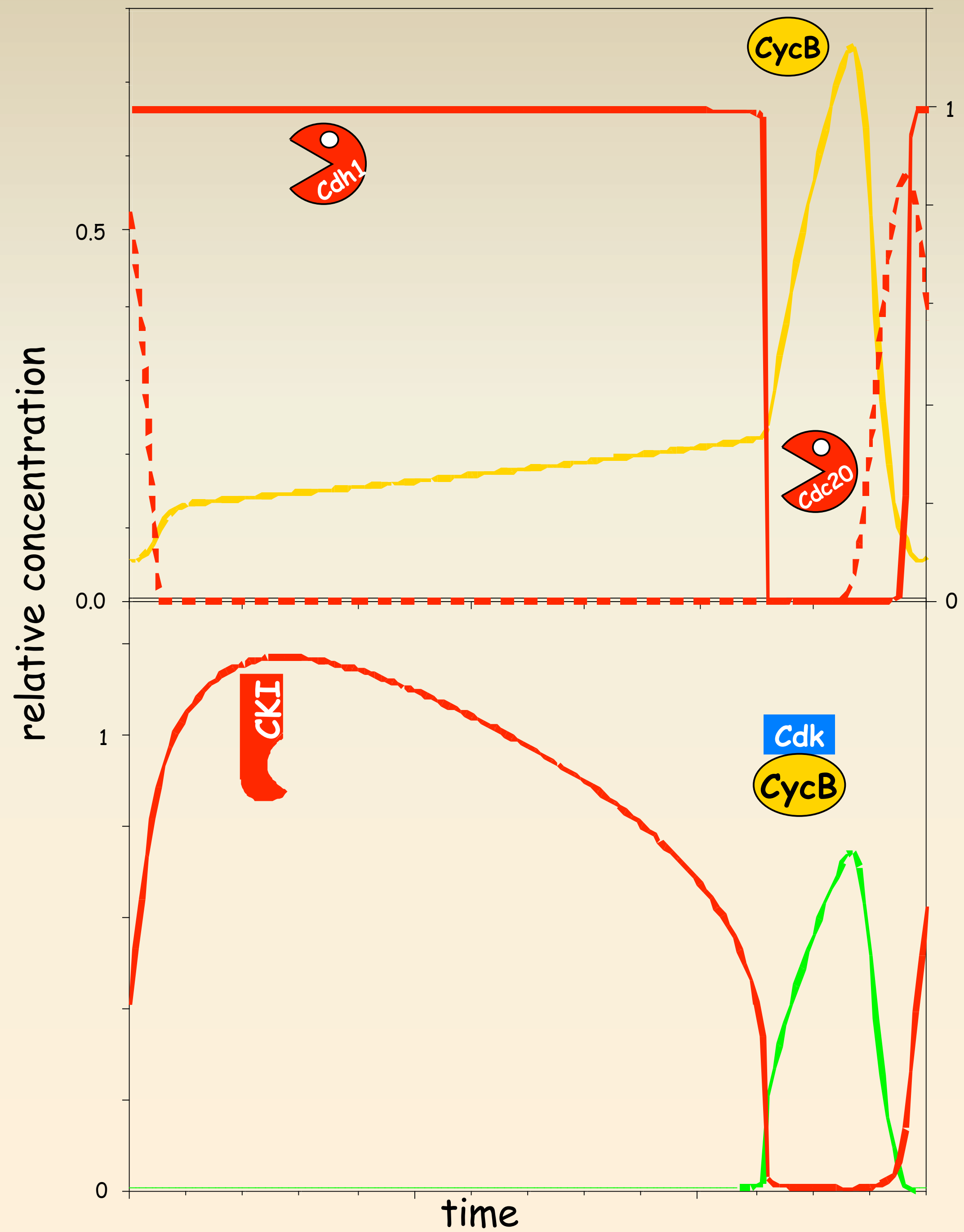
$$\dot{CKI}_T = k_9 - k_{10} \cdot CKI_T$$

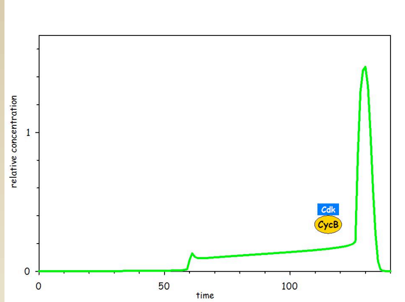
$$\dot{Trim} = k_a \cdot MPF \cdot CKI - k_d \cdot Trim - (k_2 + k_{10}) \cdot Trim$$

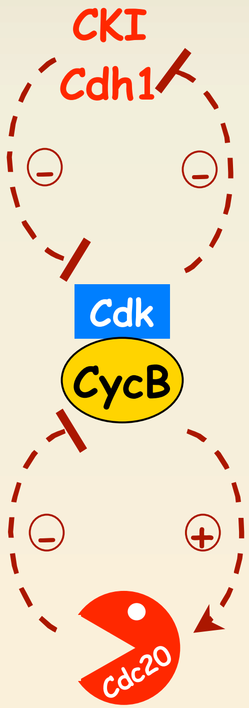
where $CKI = CKI_T - Trim$

$$\dot{MPF} = k_1 - k_2 \cdot MPF - k_a \cdot MPF \cdot CKI + k_d \cdot Trim + k_{10} \cdot Trim$$

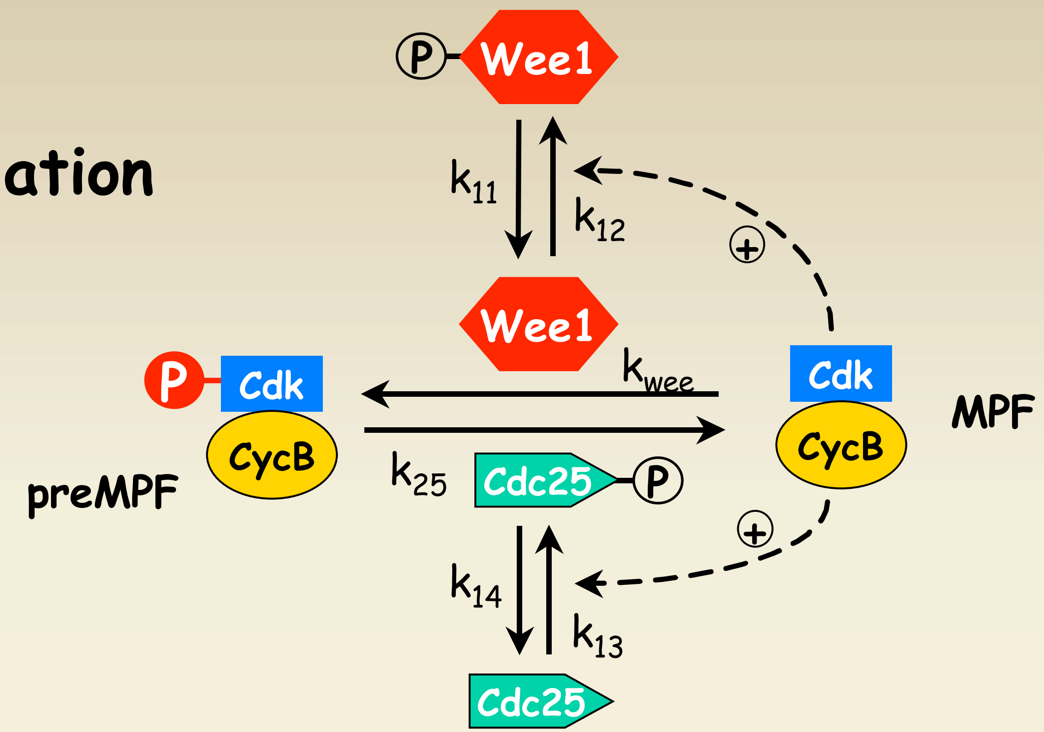
where $k_{10} = k_{10}' + k_{10}'' \cdot MPF$


CycB
Cdh1
Cdc20
CKI
Cdk
CycB
1
0.5
0.0
0
1
0
relative concentration
time


relative concentration
1
0
0
50
100
time
Cdk
CycB


CKI
Cdh1
Cdk
CycB
Cdc20

Inhibitory phosphorylation of Cdk



•

$MPF = k_1 - k_2 \cdot MPF - k_a \cdot MPF \cdot CKI + k_d \cdot Trim + k_{10} \cdot Trim - k_{wee} \cdot MPF + k_{25} \cdot pMPF$

where $k_{wee} = k_{wee}' + k_{wee}'' \cdot Wee1_A$ and $k_{25} = k_{25}' + k_{25}'' \cdot Cdc25_A$

•

$pMPF = k_{wee} \cdot MPF - k_{25} \cdot pMPF - k_2 \cdot pMPF$

$Wee1^A = k^{11} \; 1 - Wee1^A J^{11} + 1 - Wee1^A - (k^{12\prime} + k^{12\prime\prime} \cdot MPF) \; Wee1^A J^{12}$

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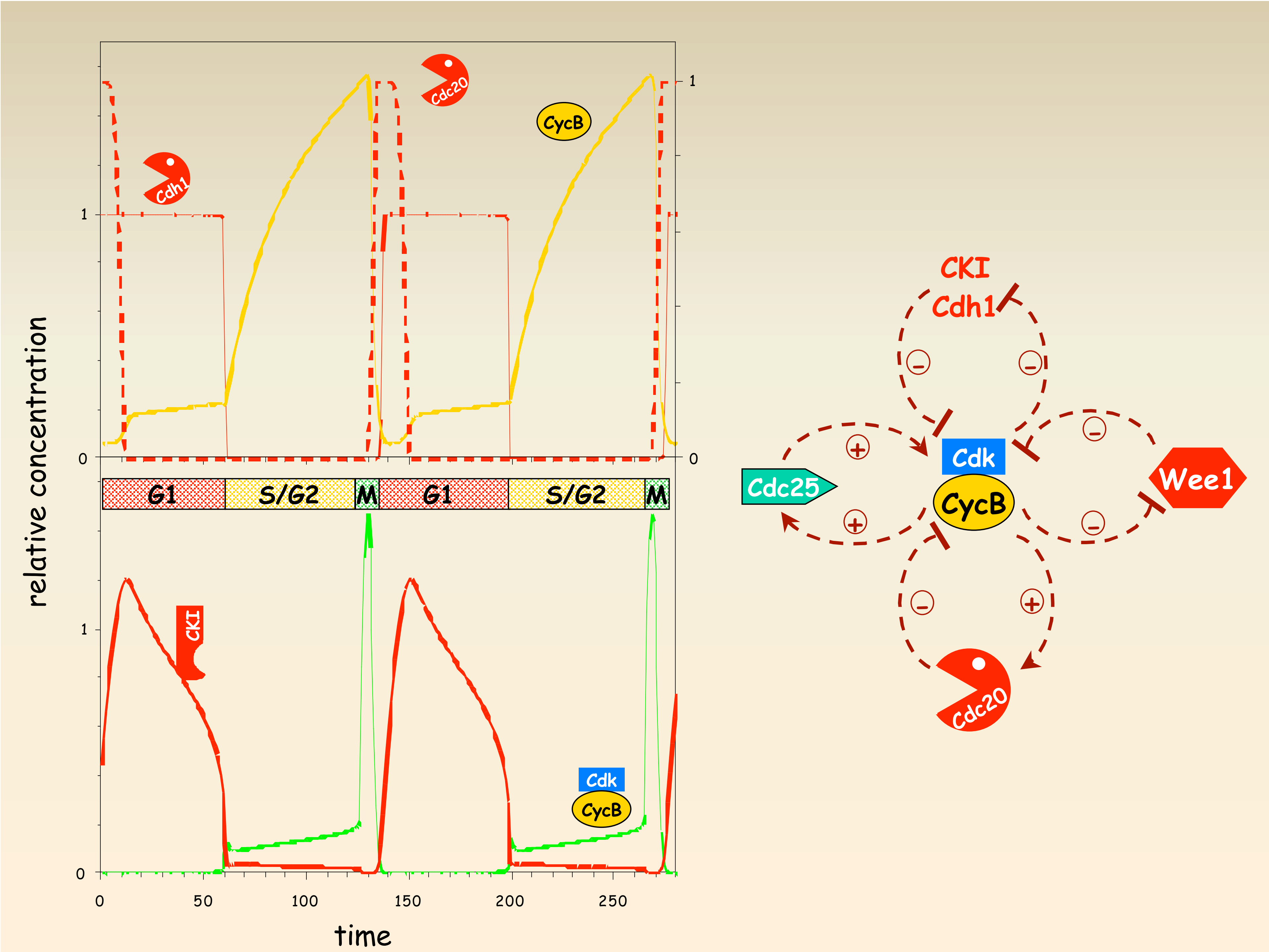

relative concentration
time
0
50
100
150
200
250
1
0
1
0
1
0
Cdh1
Cdc20
CycB
CKI
Cdk
CycB
G1
S/G2
M
G1
S/G2
M
CKI
Cdh1
Cdk
CycB
Cdc25
Wee1
Cdc20

- $\dot{MPF} = k_1 - k_2 \cdot MPF - k_a \cdot MPF \cdot CKI + k_d \cdot Trim + k_{10} \cdot Trim - k_{wee} \cdot MPF + k_{25} \cdot pMPF$
- $\dot{pMPF} = k_{wee} \cdot MPF - k_{25} \cdot pMPF - k_2 \cdot pMPF$
- $\dot{CKI_T} = k_9 - k_{10} \cdot CKI_T$
- $\dot{Trim} = k_a \cdot MPF \cdot CKI - k_d \cdot Trim - (k_2 + k_{10}) \cdot Trim$

Cdh1A = k3 1 - Cdh1AJ3 + 1 - Cdh1A - k4 · MPF Cdh1AJ4 + Cdh1A IEA = k5 · MPF 1 -

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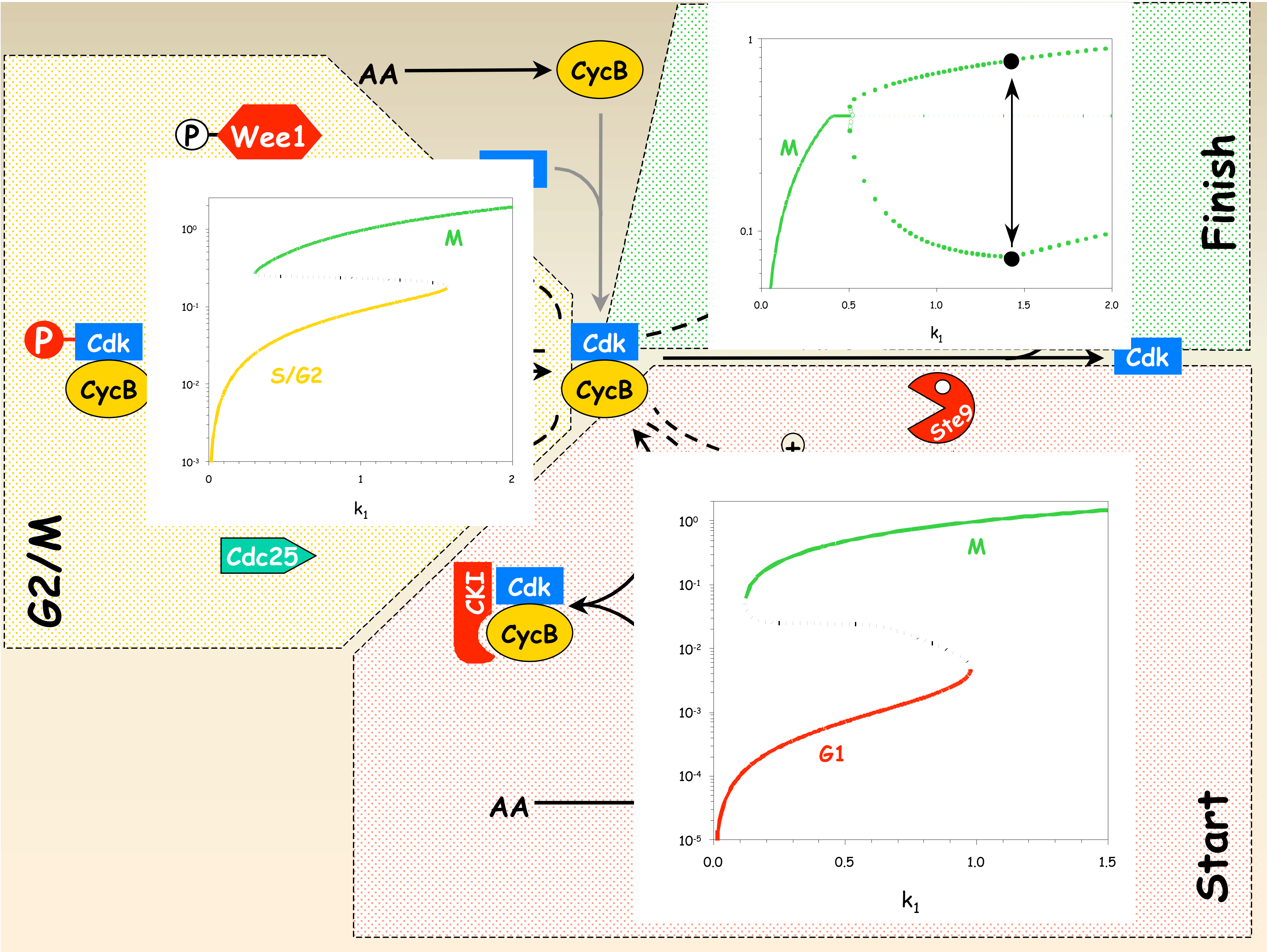
where $k_2 = k_2' + k_2'' \cdot Cdh1_A + k_2''' \cdot Cdc20_A$

$k_{10} = k_{10}' + k_{10}'' \cdot MPF$

$k_{wee} = k_{wee}' + k_{wee}'' \cdot Wee1_A$

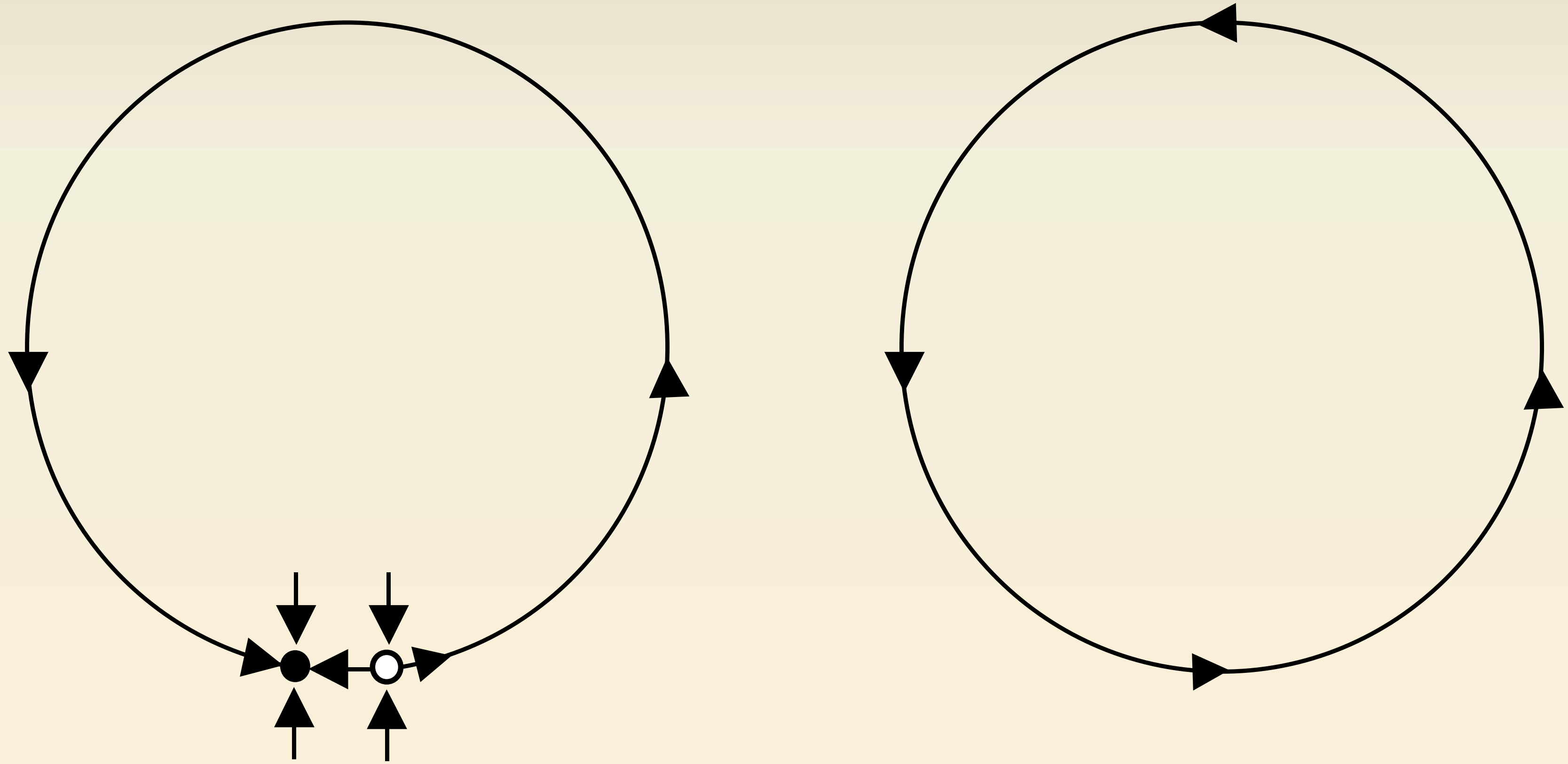
$k_{25} = k_{25}' + k_{25}'' \cdot Cdc25_A$

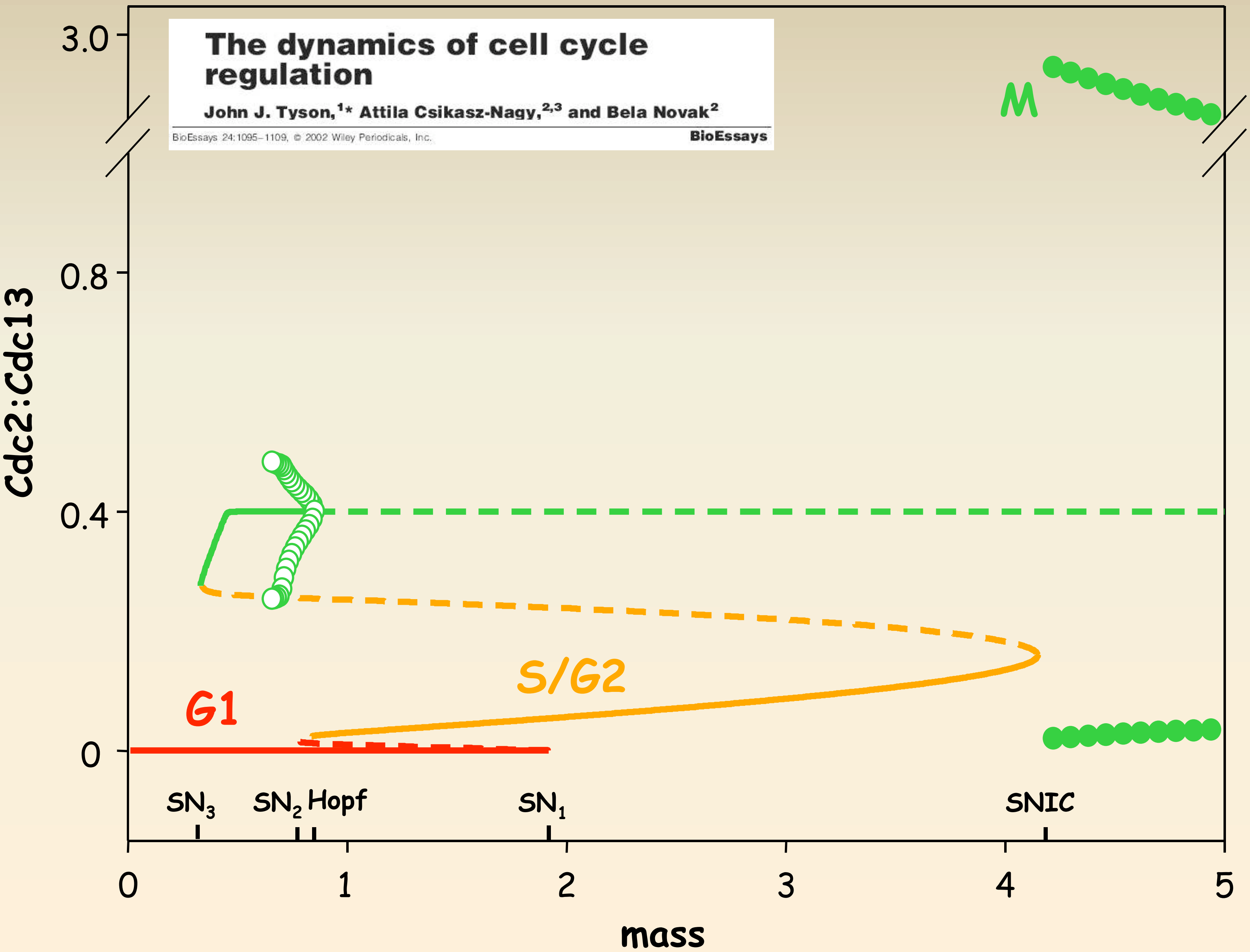
$CKI = CKI_T - Trim$

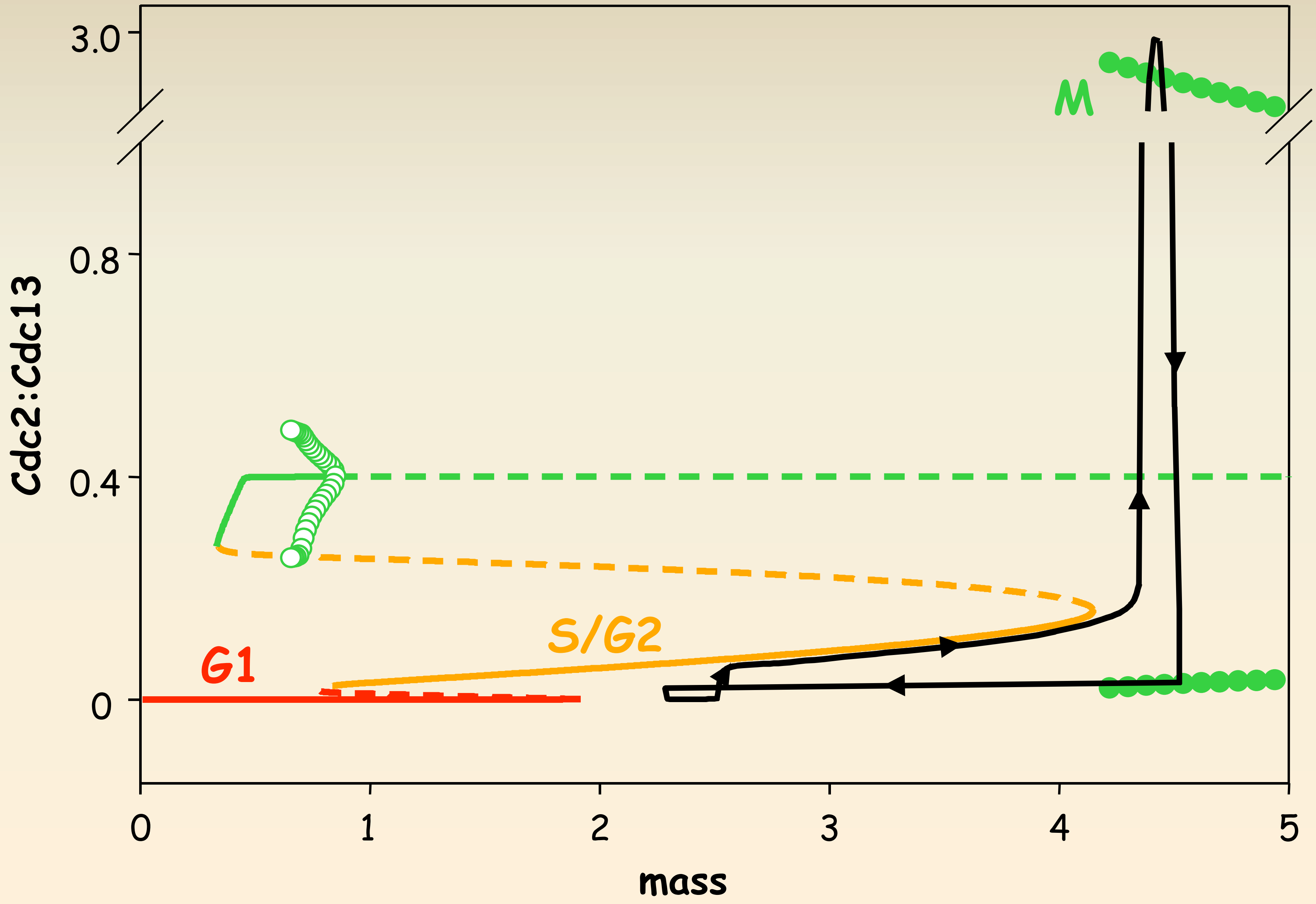


AA
CycB
P
Wee1
P
Cdk
CycB
G2/M
Cdc25
10^0
10^{-1}
10^{-2}
10^{-3}
0
1
2
k_1
M
S/G2
Cdk
CycB
1
0.1
0.0
0.5
1.0
1.5
2.0
k_1
M
Finish
Cdk
Ste9
CKI
Cdk
CycB
AA
10^0
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^{-5}
0.0
0.5
1.0
1.5
k_1
M
G1
Start

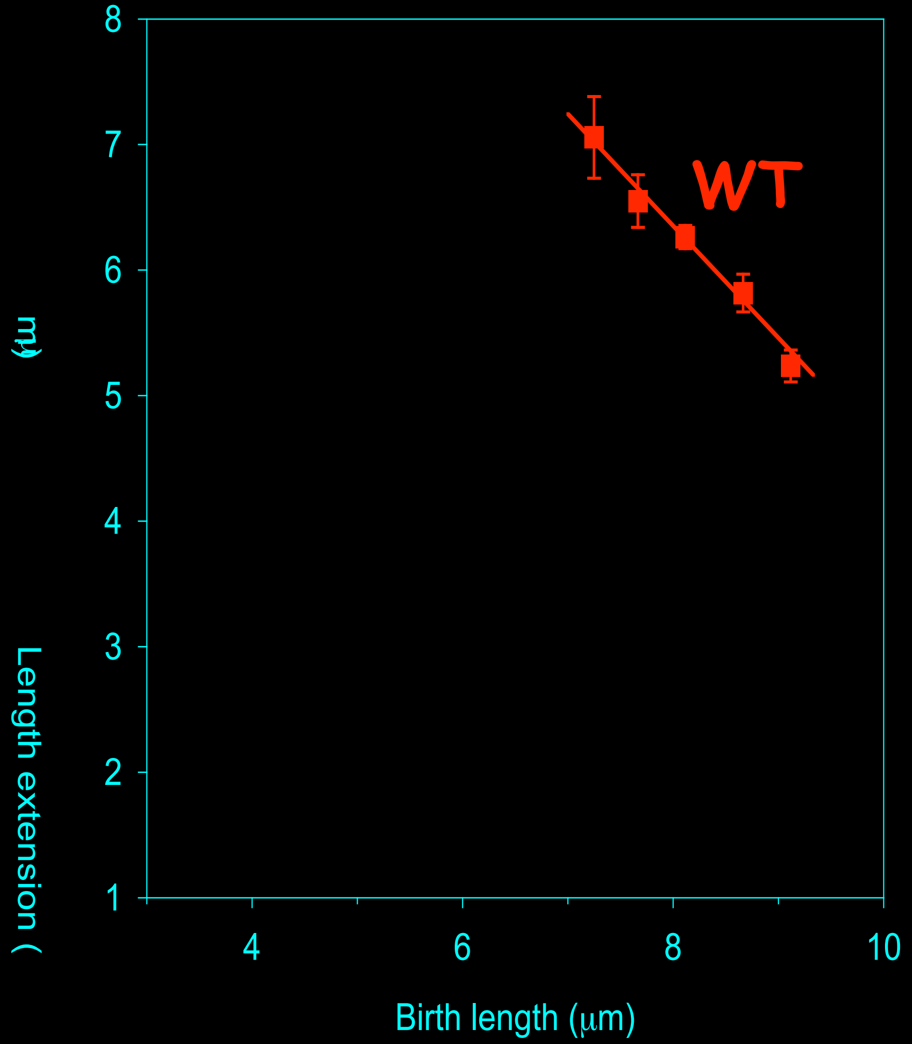
SNIC (saddle-node on infinite circle) bifurkáció




The dynamics of cell cycle regulation
John J. Tyson,[1]* Attila Csikasz-Nagy,[2,3] and Bela Novak[2]
BioEssays 24:1095–1109, © 2002 Wiley Periodicals, Inc.
BioEssays
3.0
0.8
0.4
0
Cdc2:Cdc13
M
S/G2
G1
SN3
SN2
Hopf
SN1
SNIC
0
1
2
3
4
5
mass


3.0
0.8
0.4
0
Cdc2:Cdc13
M
S/G2
G1
0
1
2
3
4
5
mass

Balanced growth and division: size control

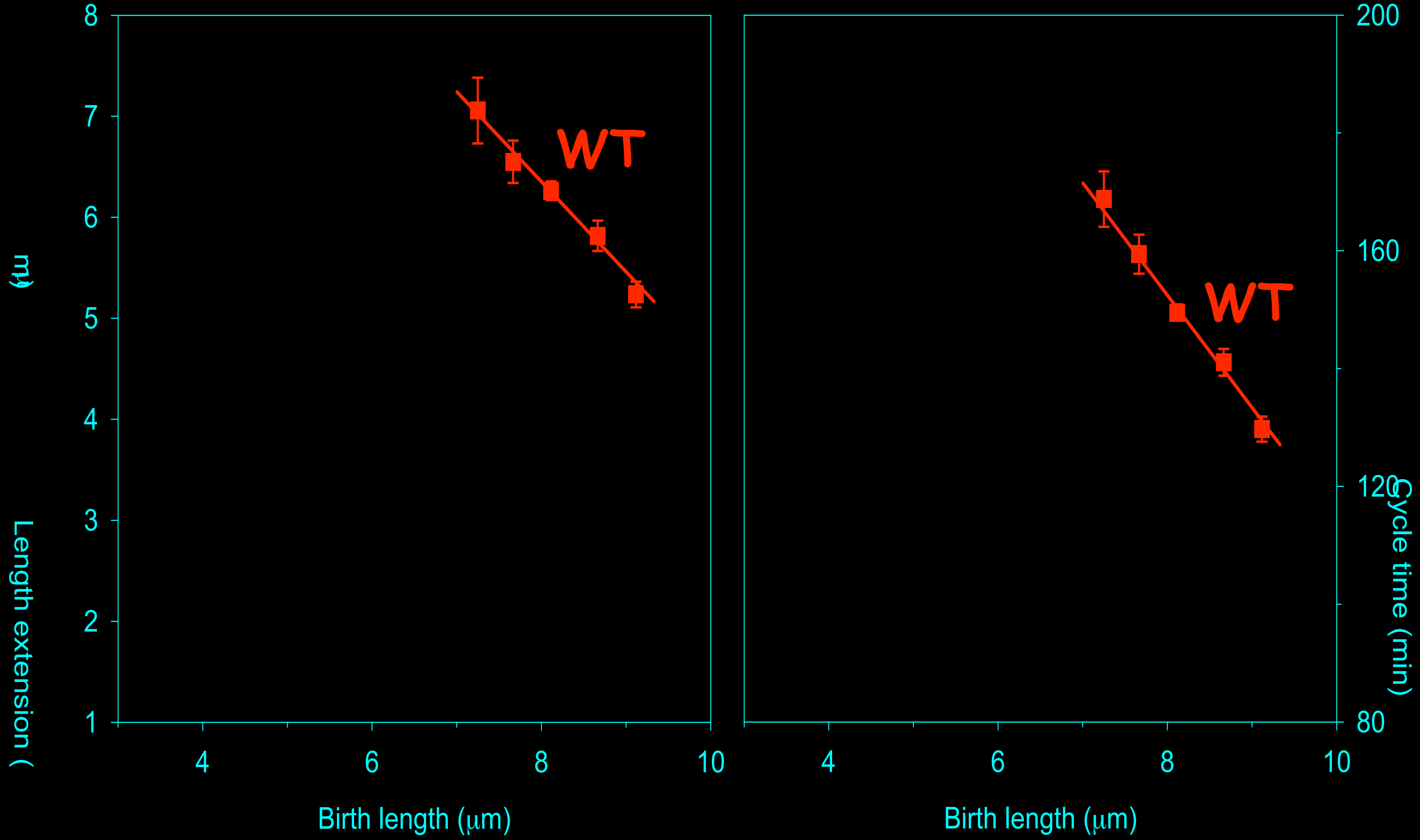


Journal of Cell Science 109, 2947-2957 (1996)

The size control of fission yeast revisited

A. Sveiczer[1], B. Novak[1,*] and J. M. Mitchison[2]

Balanced growth and division: size control



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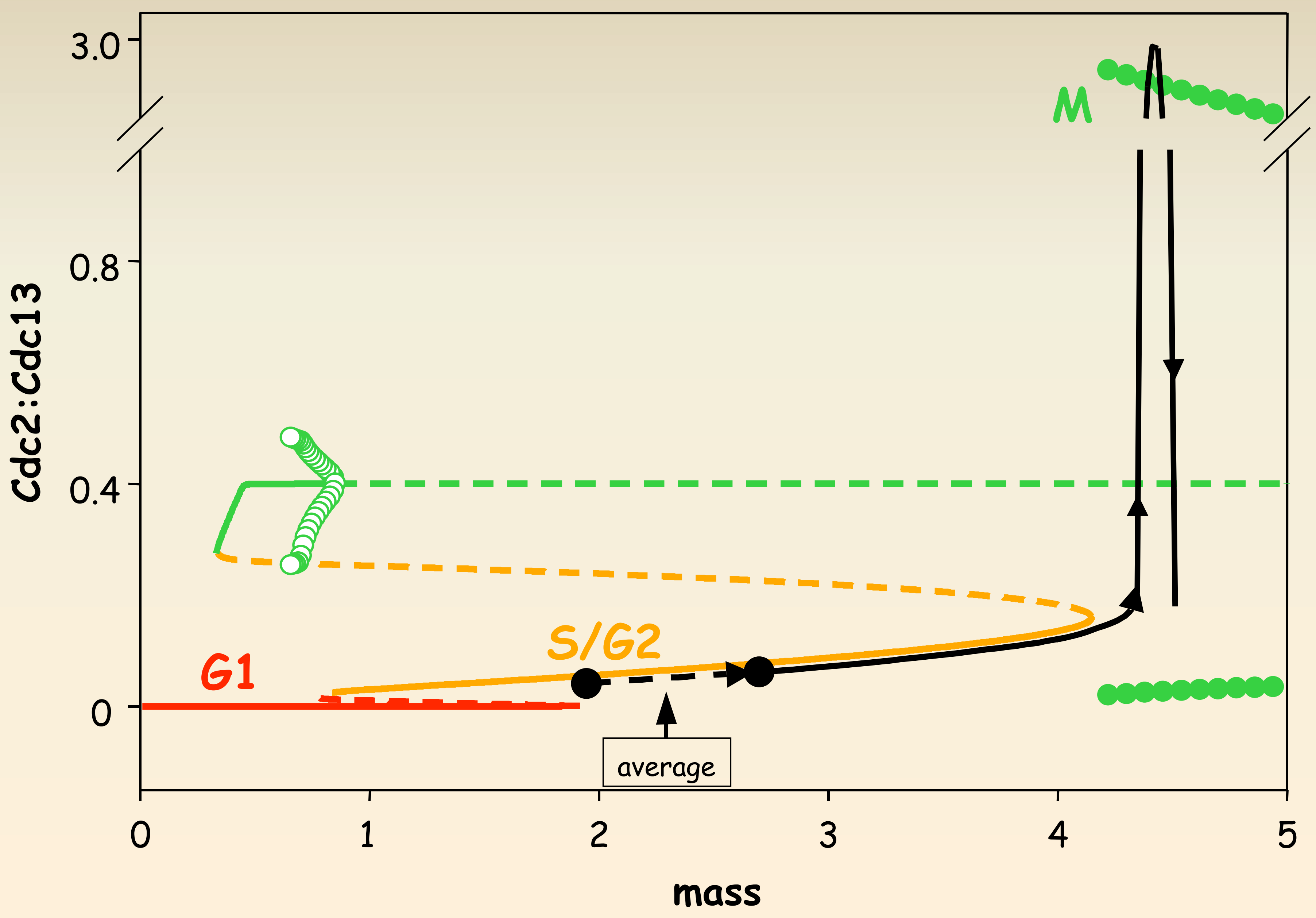
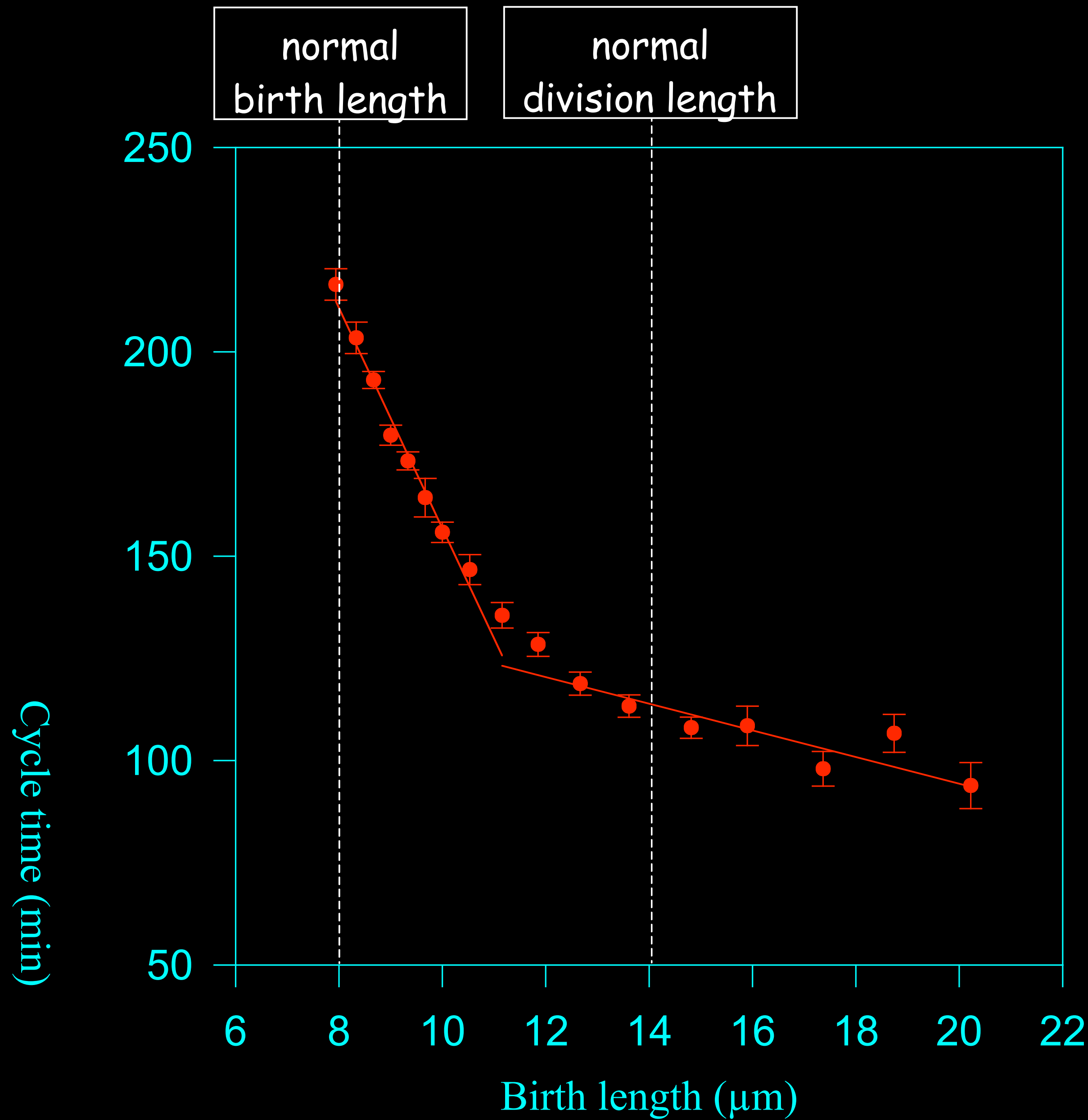
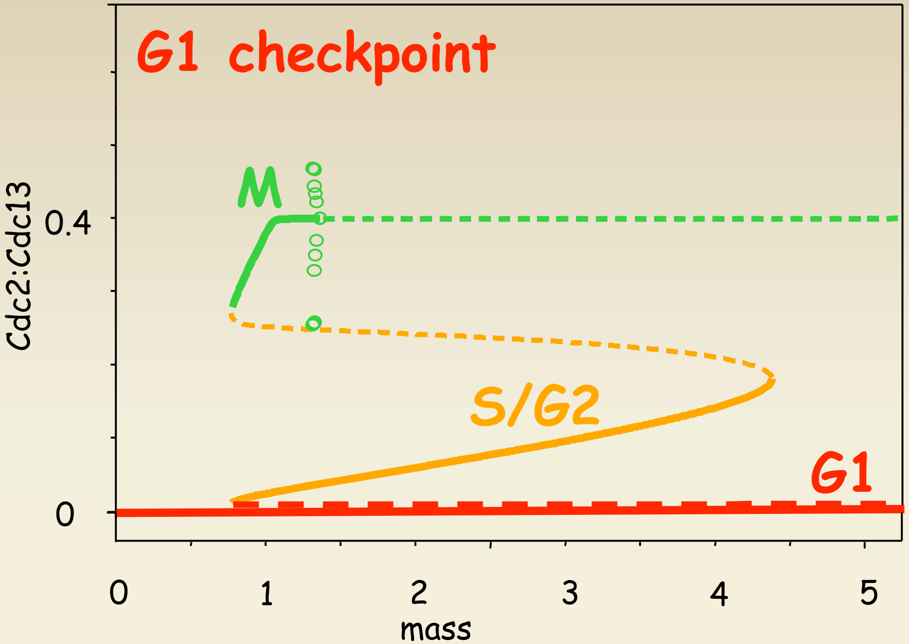


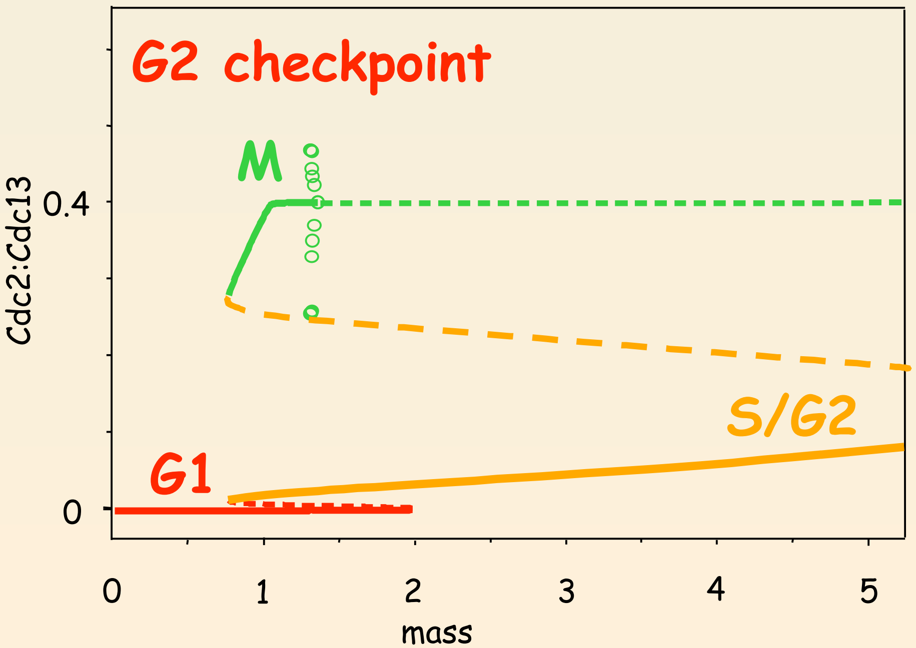
3.0
0.8
0.4
0
Cdc2:Cdc13
M
S/G2
G1
average
0
1
2
3
4
5
mass

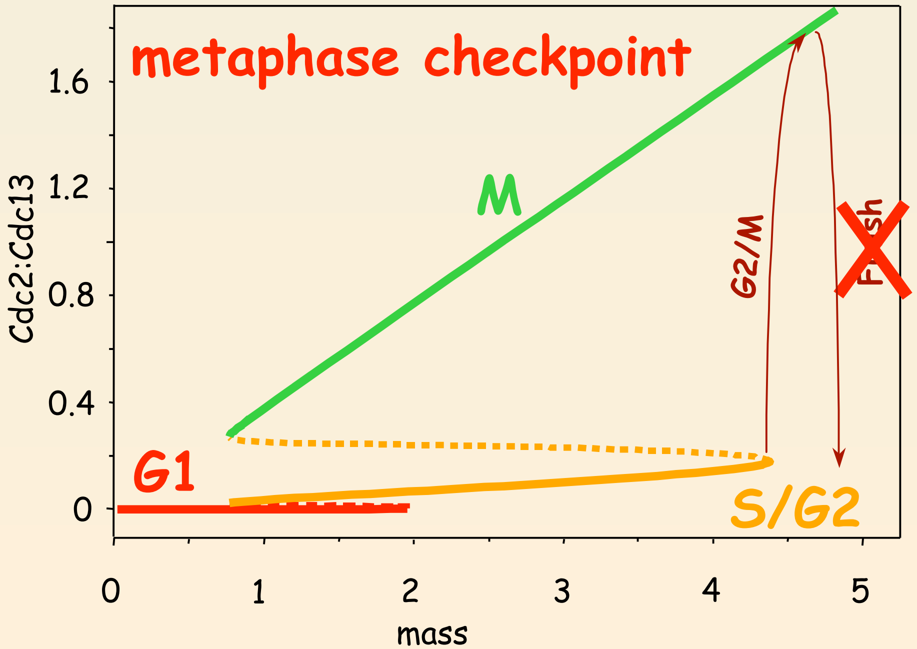
The cycle time in oversized cells



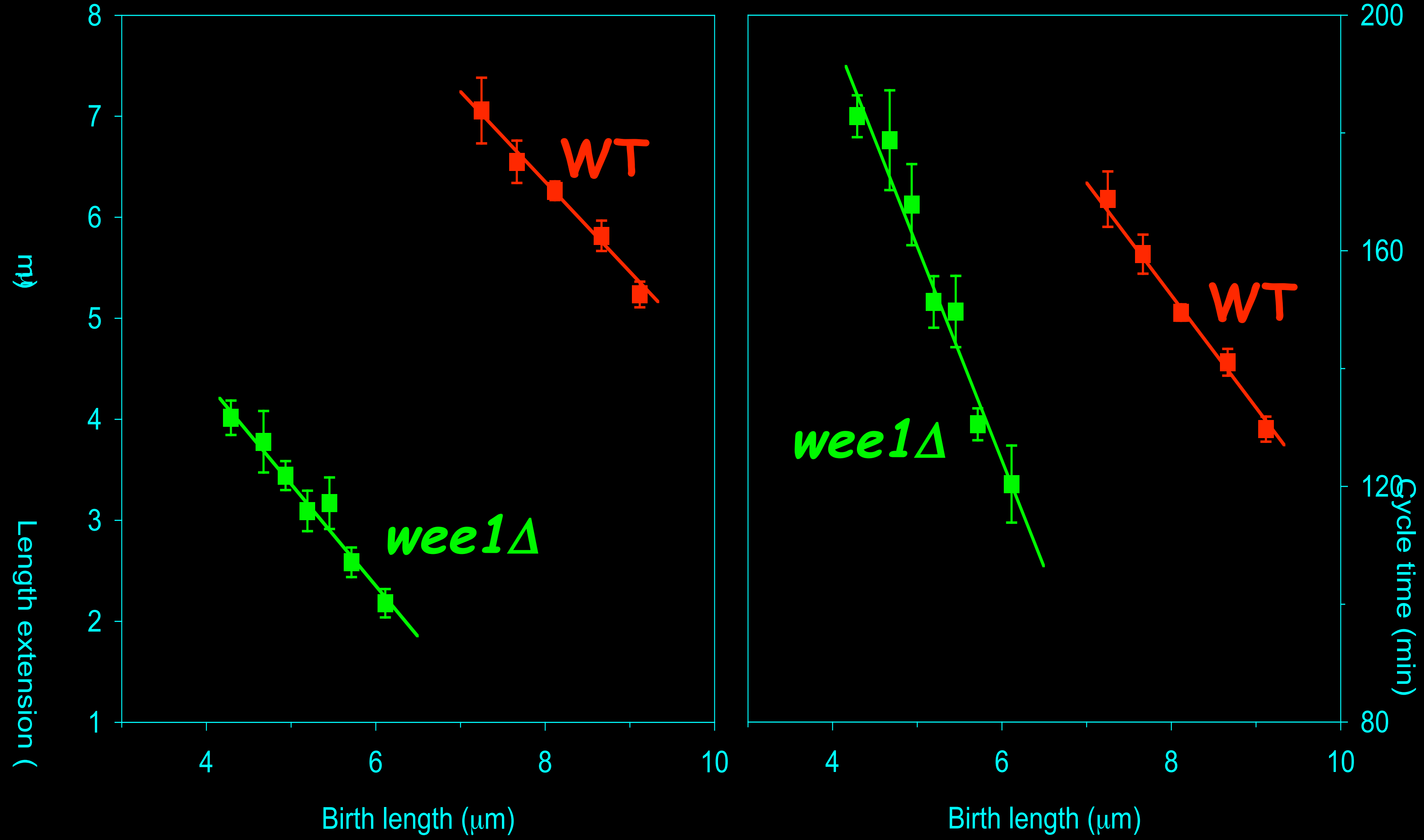
Checkpoint controls







Disruption of G2/M size control reveals a G1/S size control



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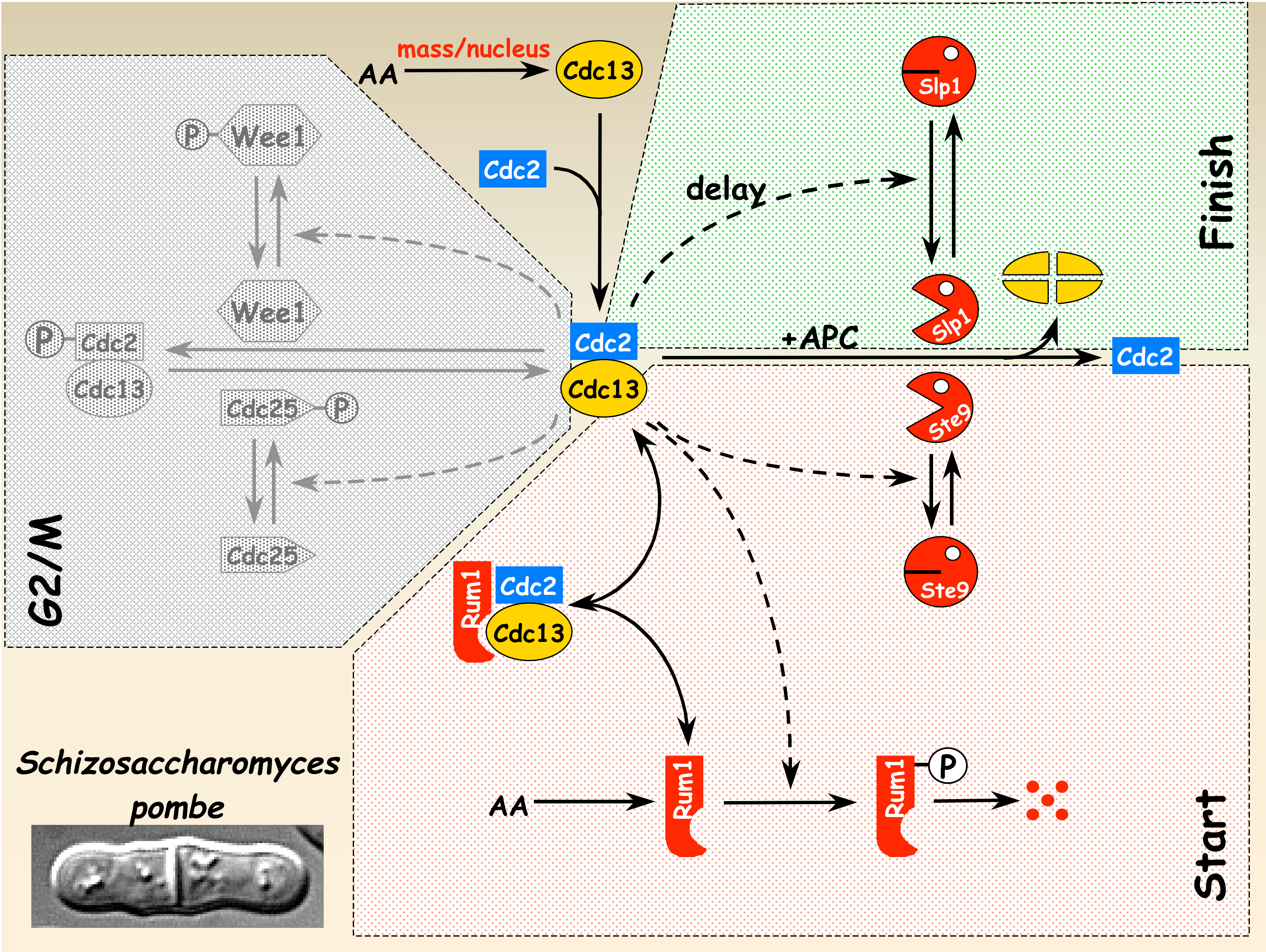
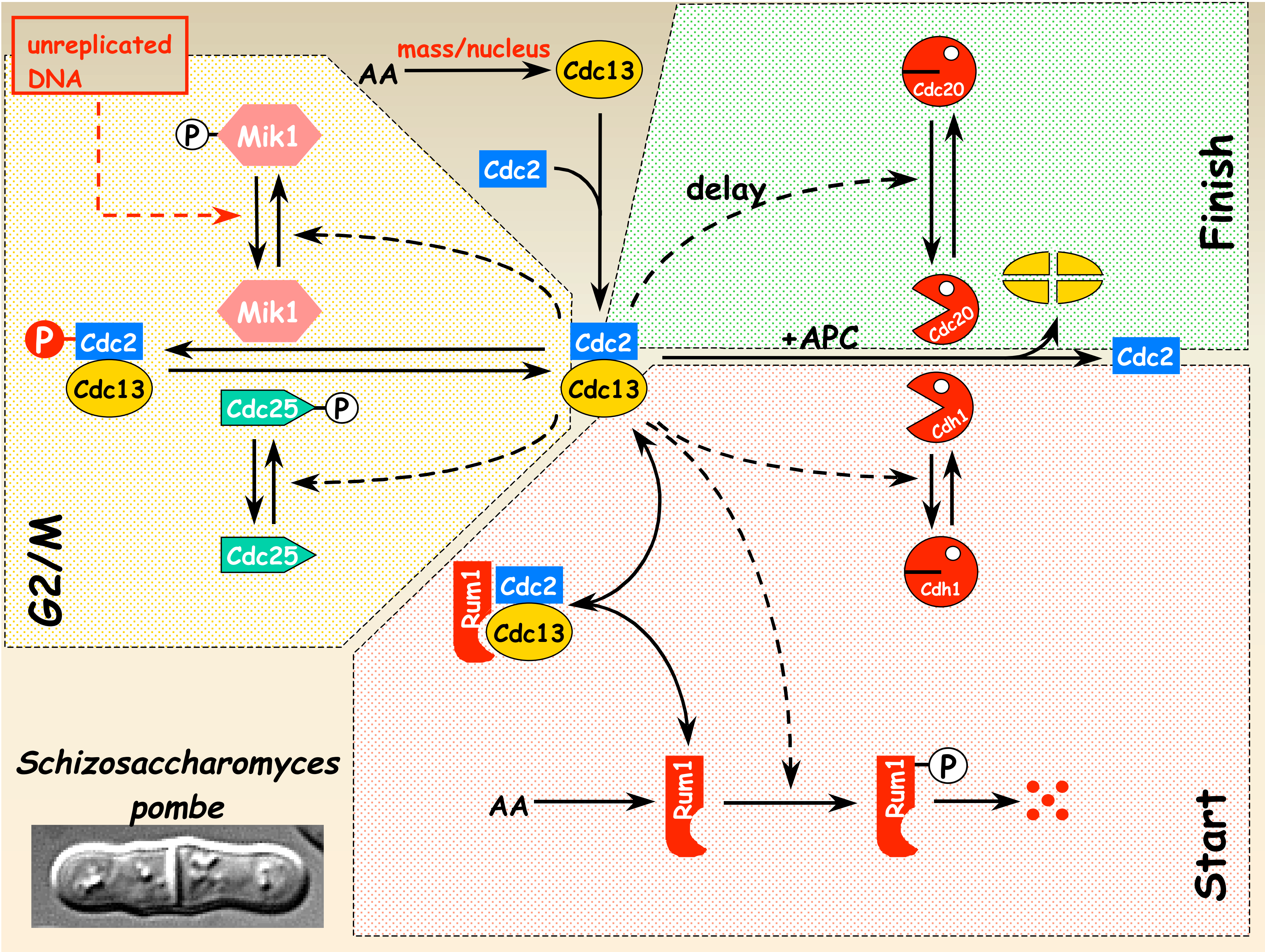
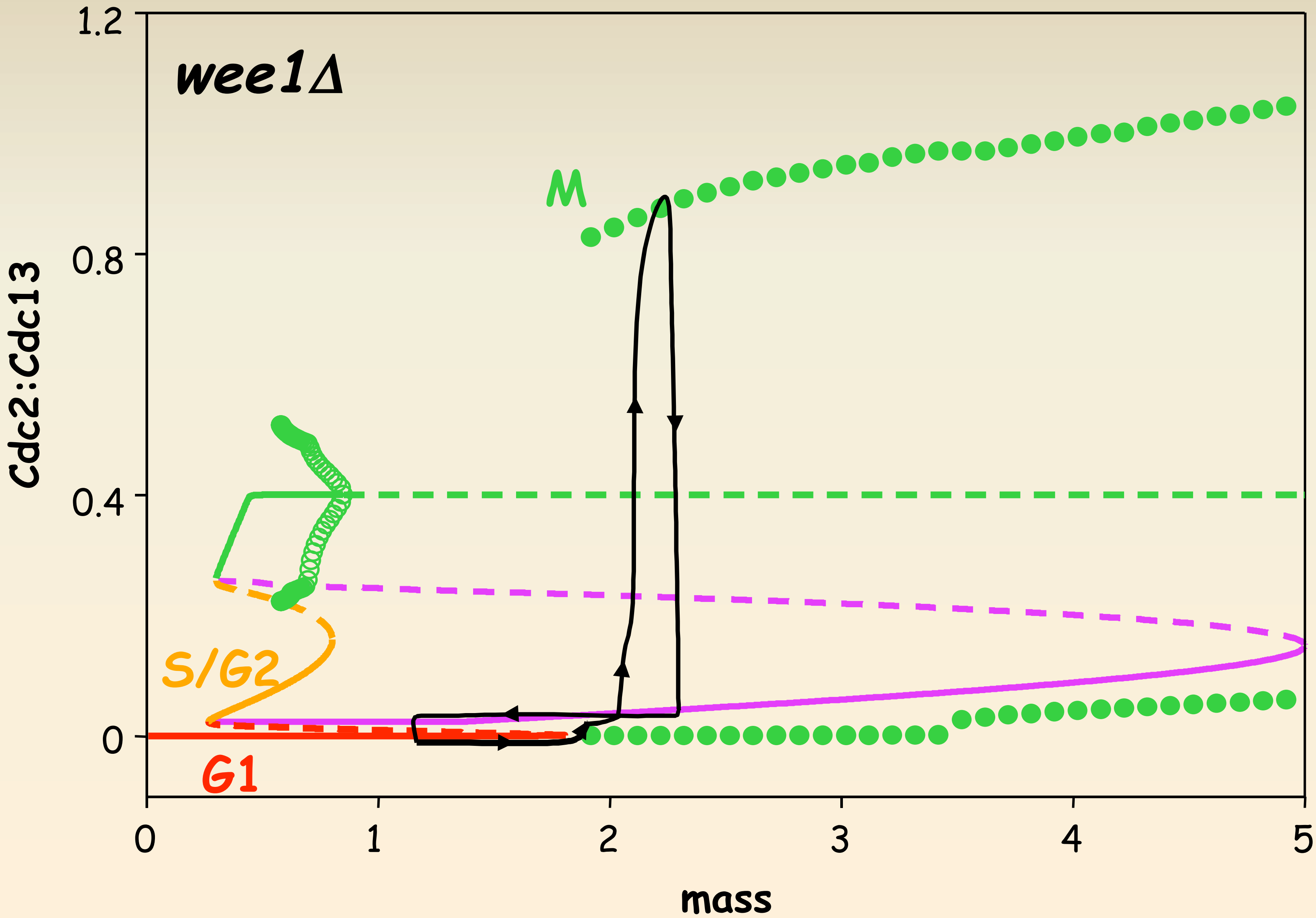


mass/nucleus
AA
Cdc13
Cdc2
P
Wee1
Wee1
delay
Slp1
Slp1
Finish
P
Cdc2
Cdc13
Cdc2
Cdc13
+APC
Cdc2
Cdc25
P
Cdc25
Ste9
Ste9
G2/M
Rum1
Cdc2
Cdc13
Schizosaccharomyces
pombe
AA
Rum1
Rum1
P
Start

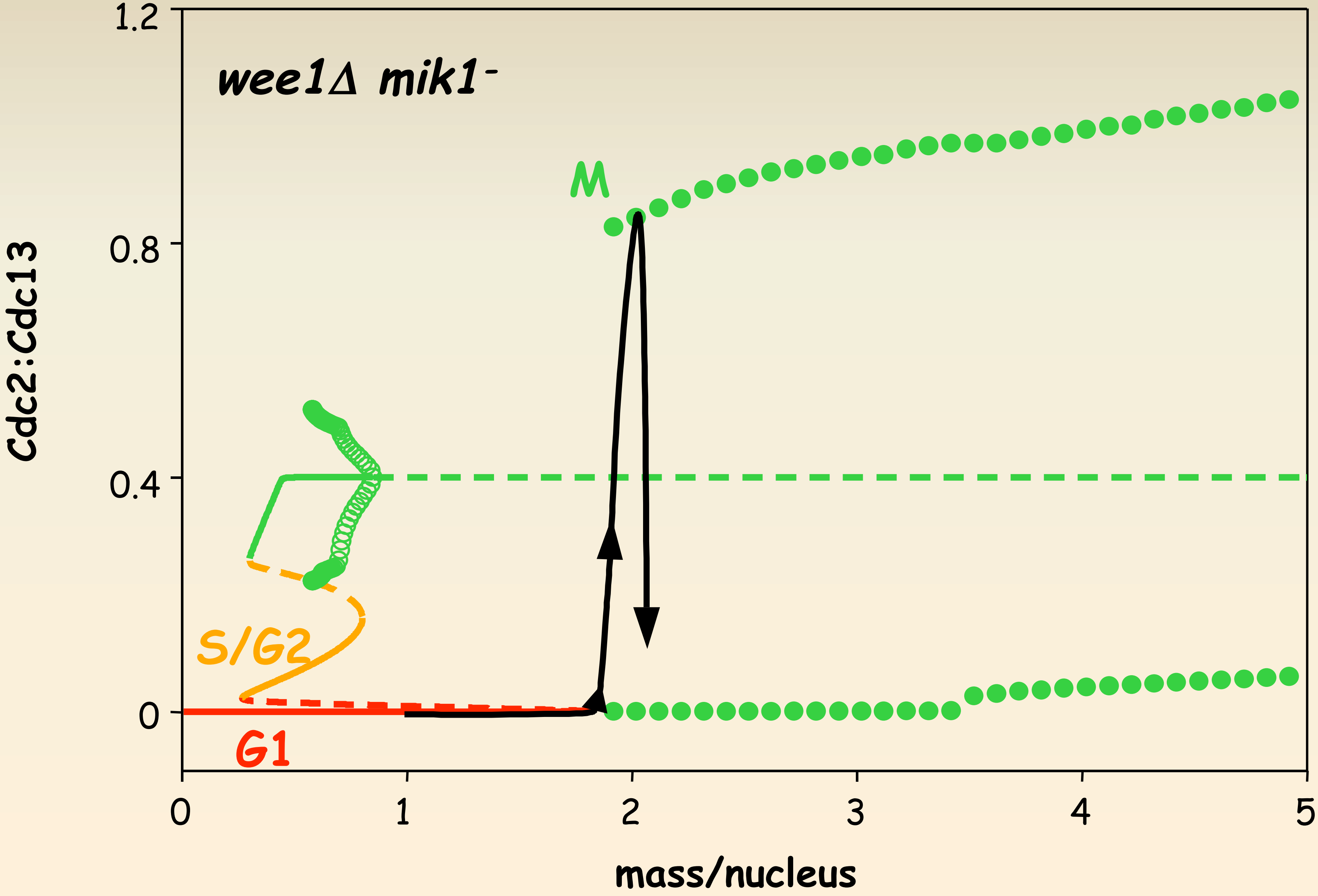


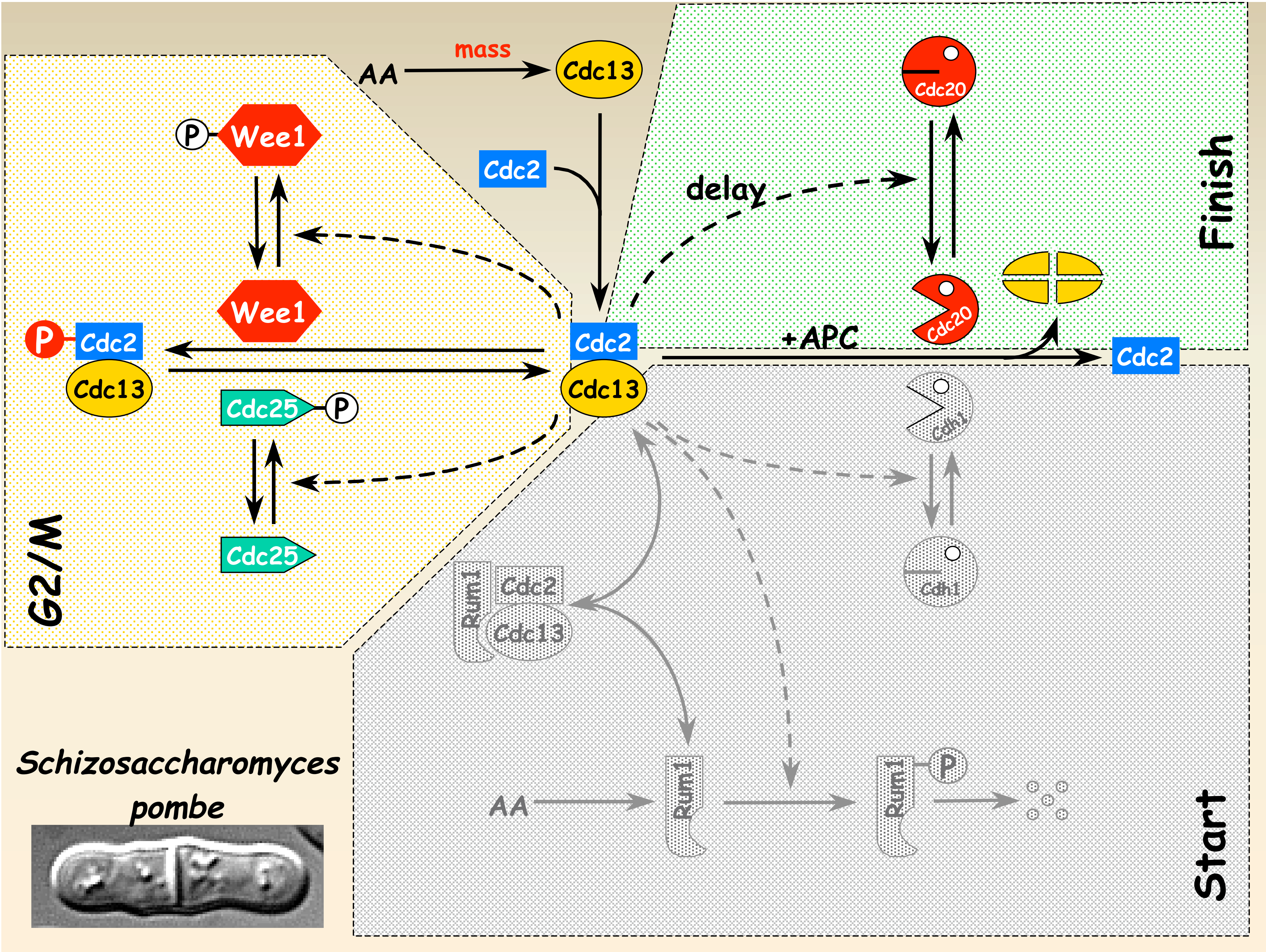
unreplicated DNA
mass/nucleus
AA
Cdc13
P
Mik1
Cdc2
delay
Mik1
Finish
Cdc20
Cdc20
P
Cdc2
Cdc13
Cdc2
Cdc13
+APC
Cdc2
Cdc25
P
Cdh1
Cdc25
Cdh1
G2/M
Rum1
Cdc2
Cdc13
Schizosaccharomyces pombe
AA
Rum1
Rum1
P
Start



wee1Δ
M
S/G2
G1
Cdc2:Cdc13
mass
1.2
0.8
0.4
0
0
1
2
3
4
5

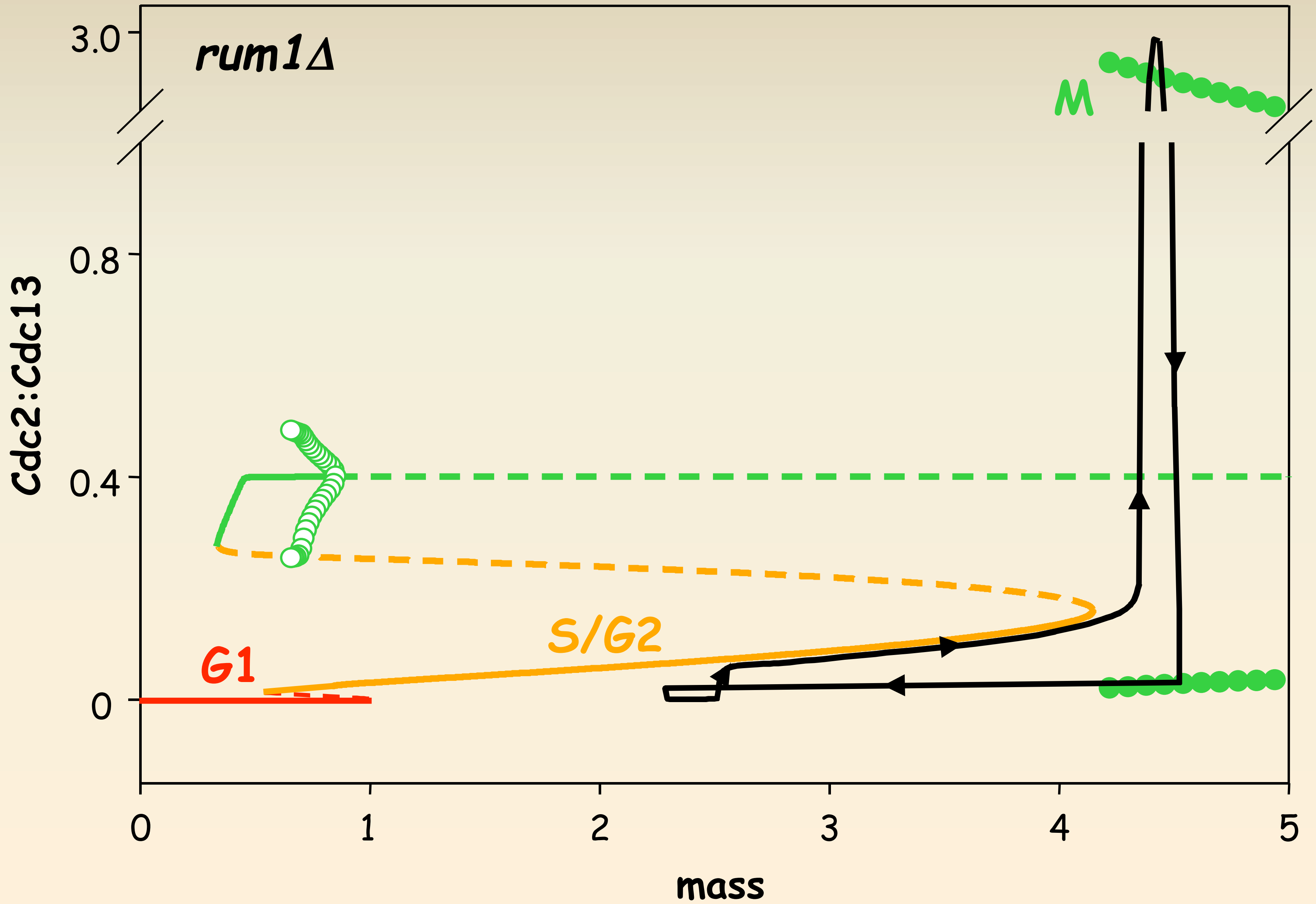
Mitotic catastrophe

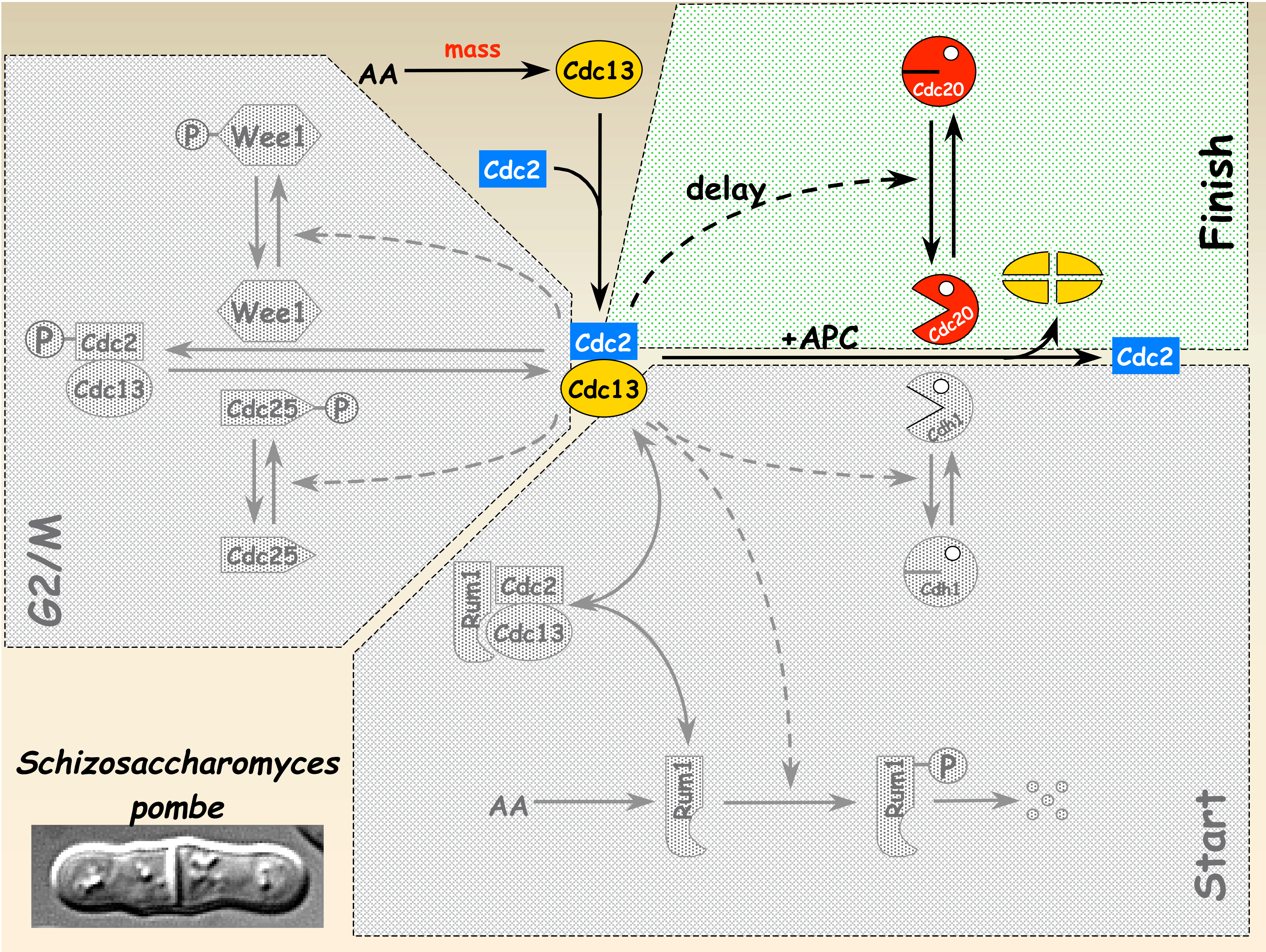




mass
AA
Cdc13
Cdc2
Wee1
P
Cdc25
delay
+APC
Cdc20
Cdh1
Rum1
Finish
Start
G2/M
Schizosaccharomyces pombe

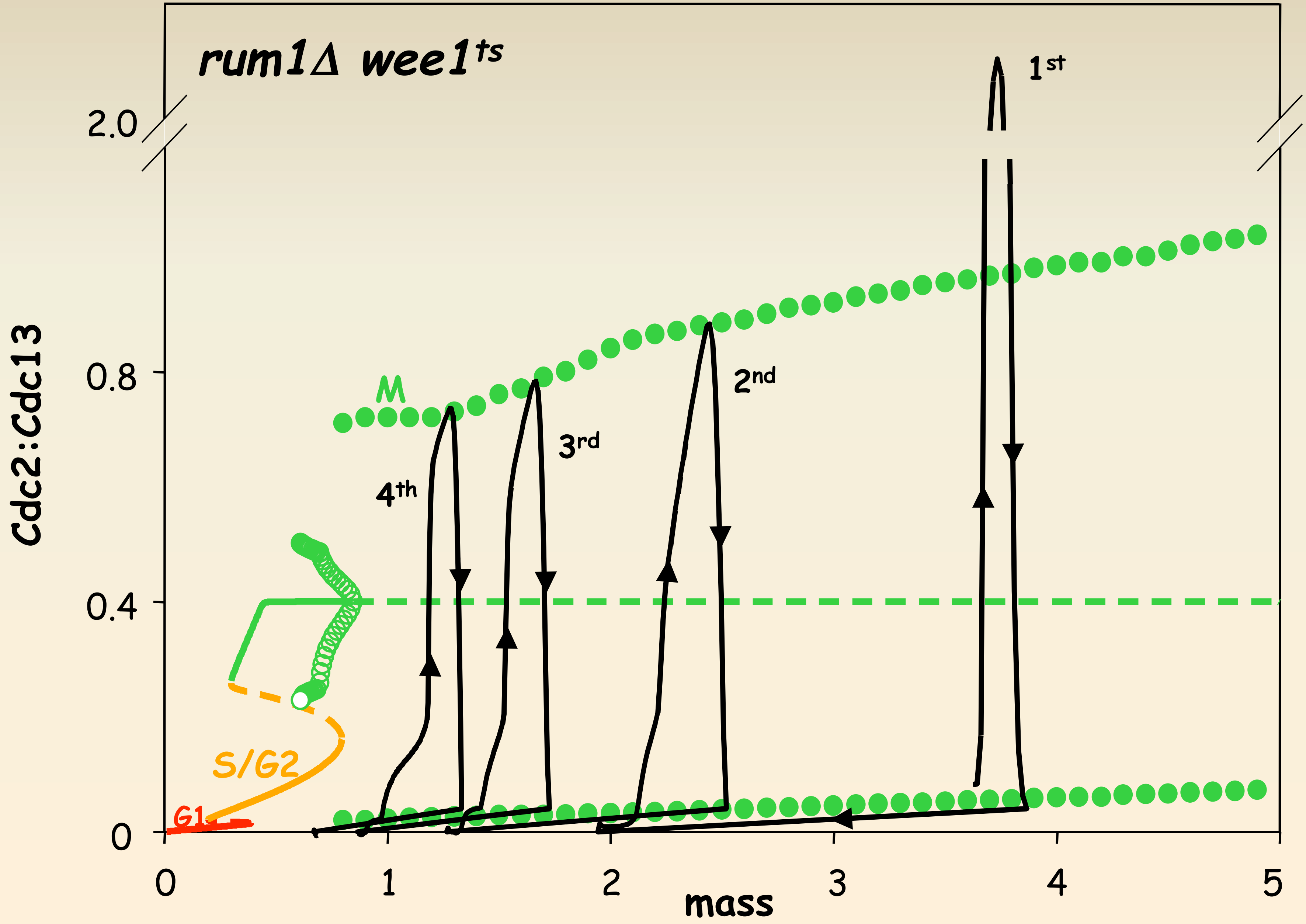
The *Start* module is not required during mitotic cycles

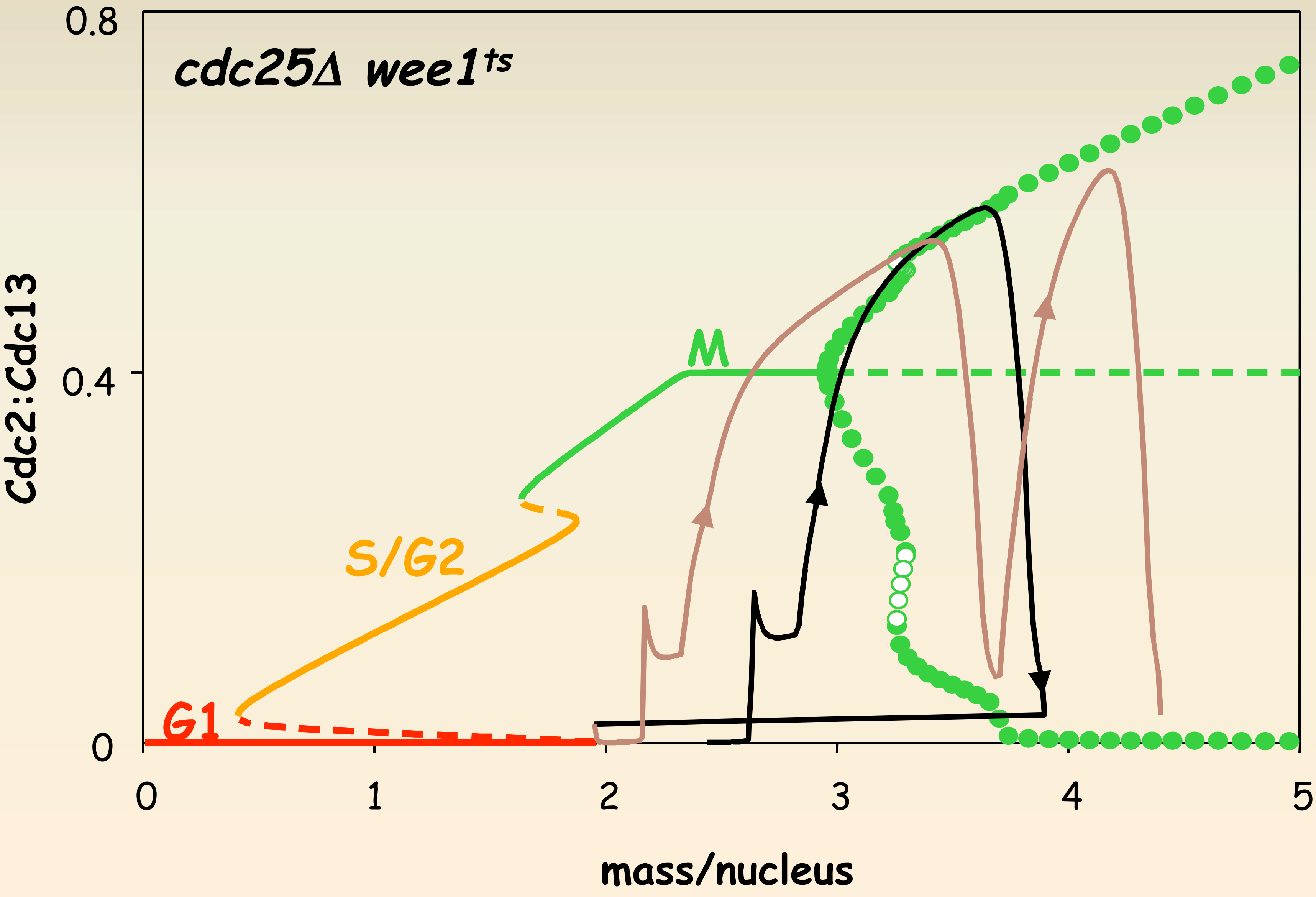




AA
mass
Cdc13
Cdc2
P
Wee1
Wee1
delay
Finish
Cdc20
Cdc20
P
Cdc2
Cdc13
Cdc2
Cdc13
+APC
Cdc2
Cdc25
P
Cdc25
Cdh1
Cdh1
G2/M
Rum1
Cdc2
Cdc13
Schizosaccharomyces
pombe
AA
Rum1
Rum1
P
Start

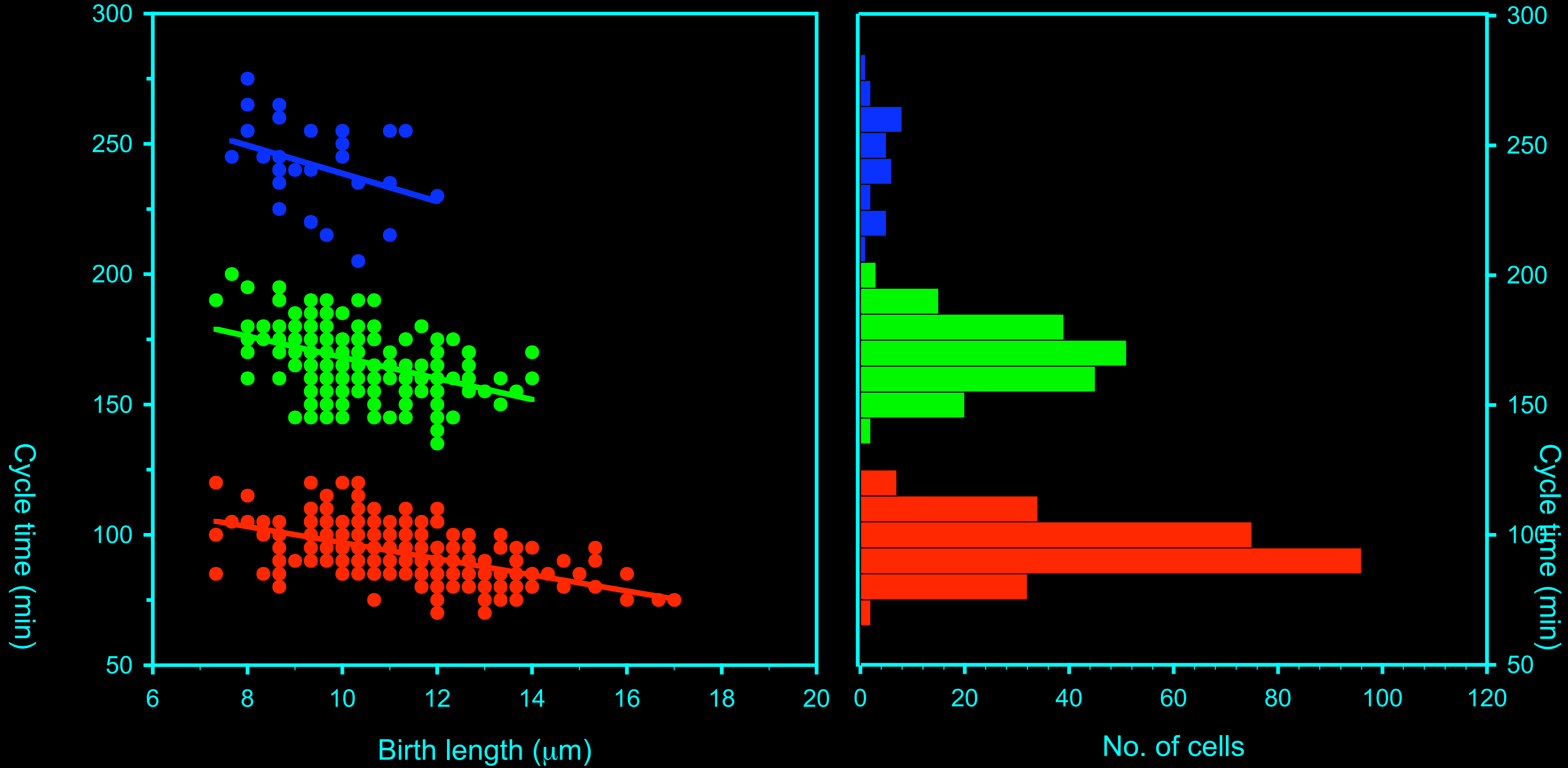
Cells become progressively smaller without size control





cdc25Δ wee1ts
0.8
0.4
0
Cdc2:Cdc13
M
S/G2
G1
0
1
2
3
4
5
mass/nucleus

cdc25Δ wee1⁻



Journal of Cell Science 112, 1085-1092 (1999)

Mitotic control in the absence of cdc25 mitotic inducer in fission yeast

A. Sveiczer[1,*], B. Novak[1] and J. M. Mitchison[2]


Paul Nurse's group
John Tyson
Ákos Sveiczer
Attila Tóth
Attila Csikász-Nagy
Béla Gy_rffy
Laurence Calzone
Kathy Chen
Andrea Ciliberto
Budapest, 2 March 2003

Homepage:

http://www.cellcycle.bme.hu/

Supporting agencies:

DARPA Defense Advanced Research Projects Agency

OTKA
Országos Tudományos Kutatási Alapprogramok
Hungarian Scientific Research Fund
Ungarische Förderungsfonds der Wissenschaftlichen Forschung

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