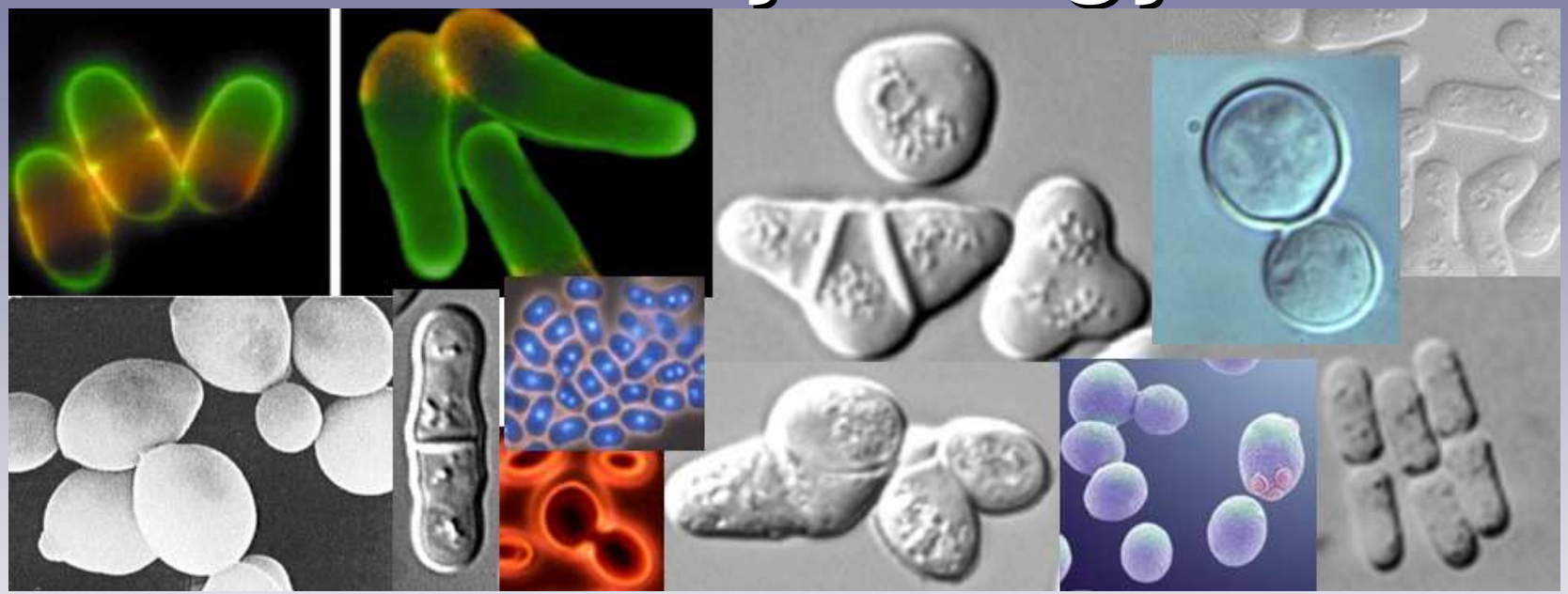
Network Dynamics and Cell Physiology



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Andrea Ciliberto

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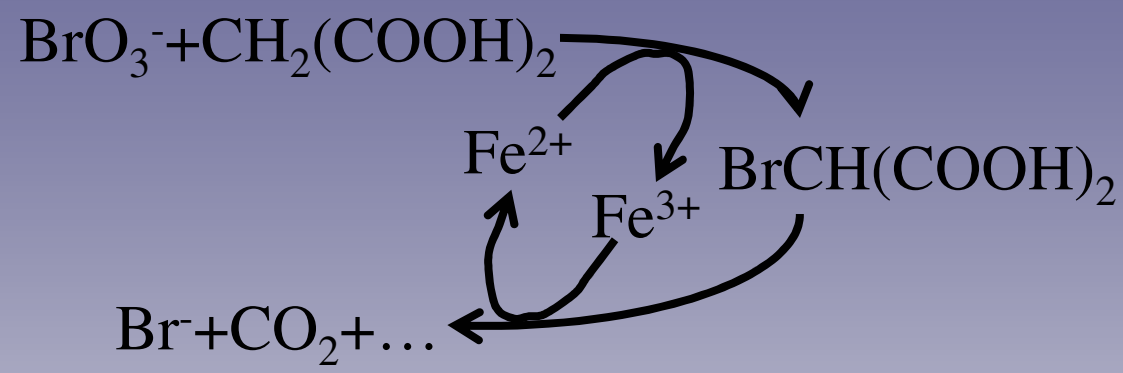
Jill Sible

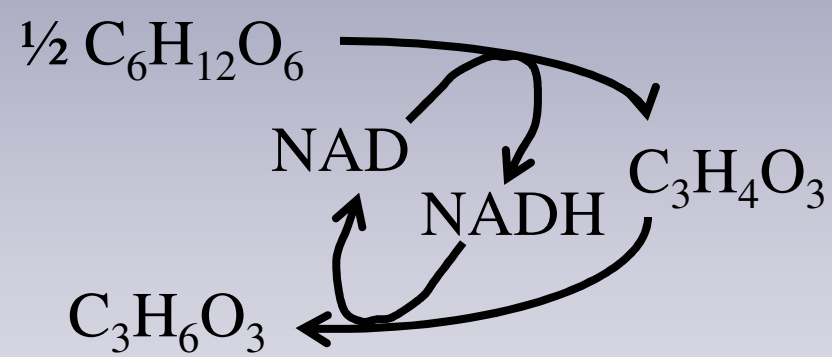
A little history…

1970's

Belousov-Zhabotinsky



Yeast Glycolysis



Higgins, Prigogine … general principles of kinetics & thermo.

Hess, Noyes … specific mechanisms of oscillations

Sonderdruck aus der ZEITSCHRIFT FÜR NATURFORSCHUNG Band 27 b, Heft 4, 1972
Verlag der Zeitschrift für Naturforschung, Tübingen

Grundschaltungen von flüssigen Automaten und Relaxationssystemen

Basic Circuits of Fluid Automata and Relaxation Systems

Otto E. Rössler

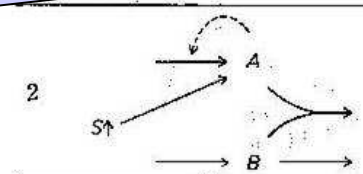
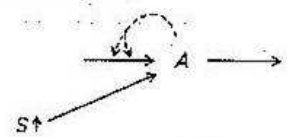
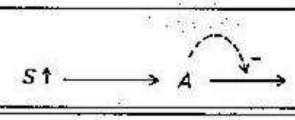
Lehrstuhl für Theoretische Chemie der Universität Tübingen (Prof. Dr. F. F. Seelig)

(Z. Naturforsch. 27 b, 333—343 [1972]; eingegangen am 21. Dezember 1971)

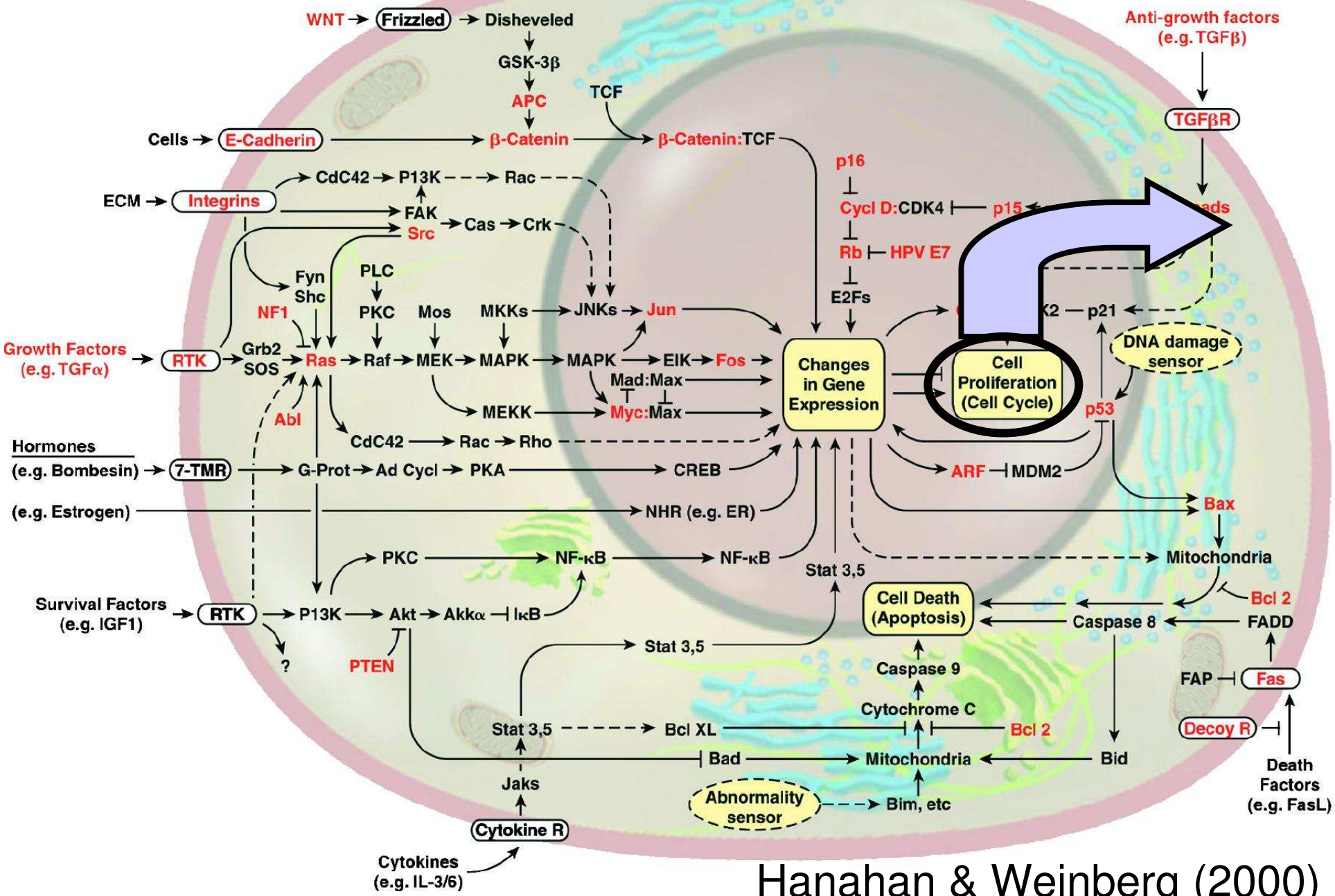
Homogeneous reaction systems showing automatic dropping-down behaviour have become known only recently. A synopsis of the so far devised basic circuits (i. e. prototype reaction systems) is presented. It is observed that the abstract design of these systems follows especially simple
They can be composed after the building-block principle from simple
accordance with the mathematical theory of
of the presented class of

In this manner, the class of chemical switching networks will be promising candidates for a possible new technology of chemical reaction systems.

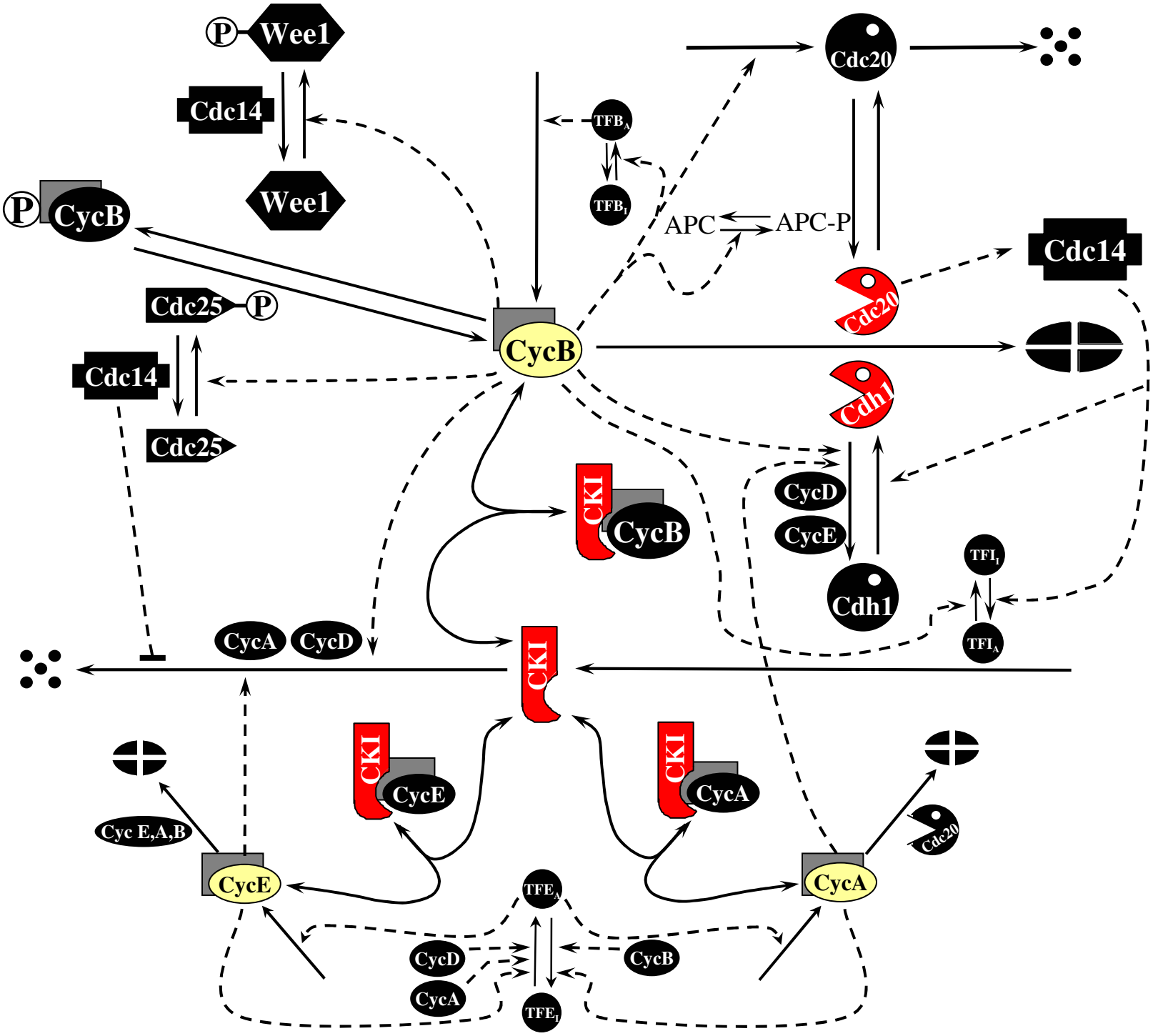
Semjonow 1934 [18]; Higgins 1967 [19]

2		$\dot{a}=k_1 a-k_2 a b$ $\dot{b}=k_3-k_4 b-k_2 a b$	Semjonow 1934 [20]; Rössler 1971 [21]
3		$\dot{a}=k_1 a^2-k_2 a$	Higgins 1967 [22]; Karfunkel 1971 [23] (vereinfacht)
4		$\dot{a}=k_1-k_2 \frac{a}{a+K+C a^2}$	Higgins 1967 [24]

The Cell's Computer…



Hanahan & Weinberg (2000)

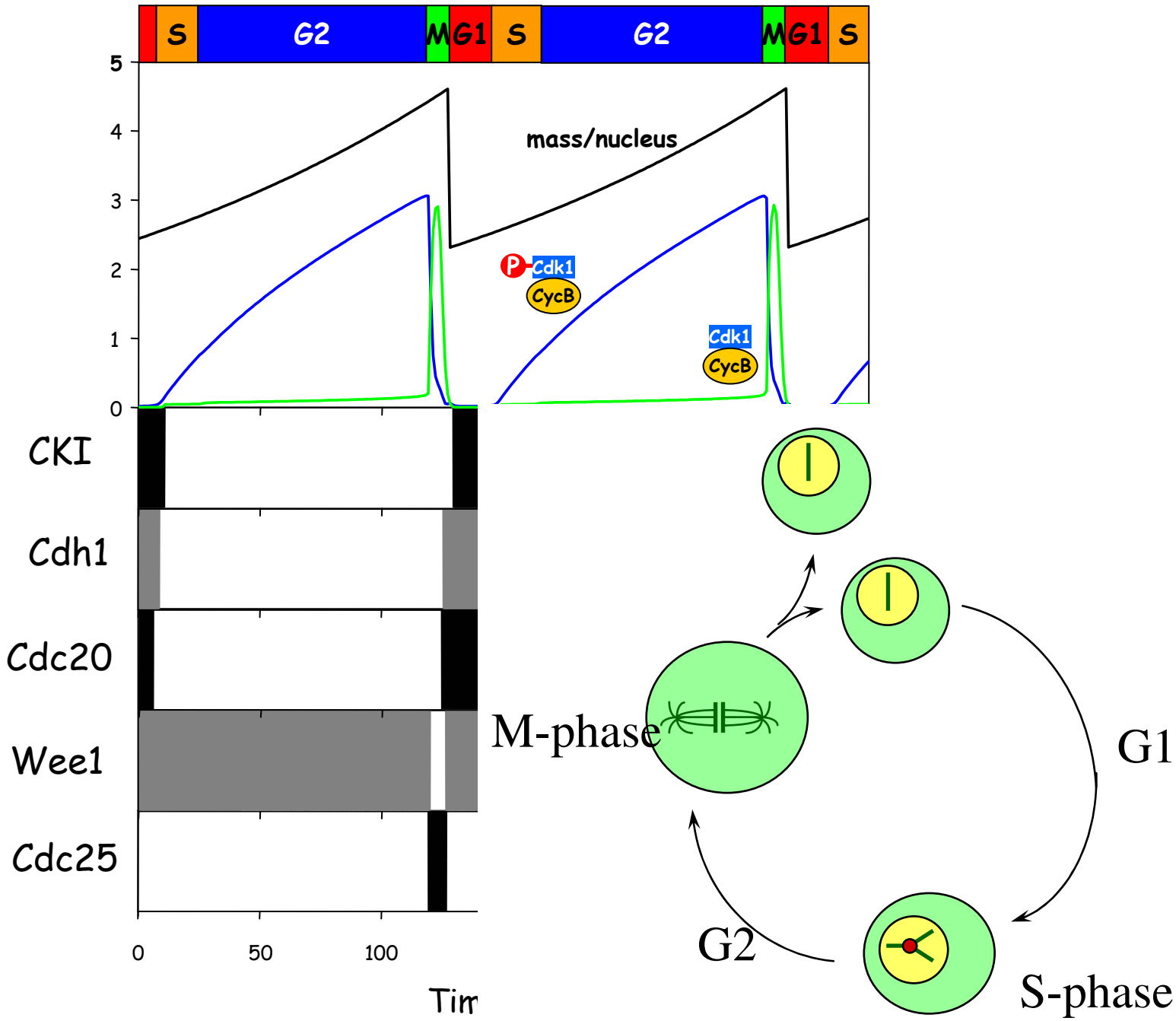

P
Wee1
Cdc14
Wee1
P
CycB
Cdc25
P
Cdc14
Cdc25
CycB
TFB$_A$
TFB$_I$
APC
APC-P
Cdc20
Cdc20
Cdc14
Cdh1
CKI
CycB
CycD
CycE
Cdh1
TFI$_I$
TFI$_A$
CycA
CycD
CKI
CKI
CycE
CKI
CycA
Cyc E,A,B
CycE
TFE$_A$
CycA
Cdc20
CycD
CycA
CycB
TFE$_I$

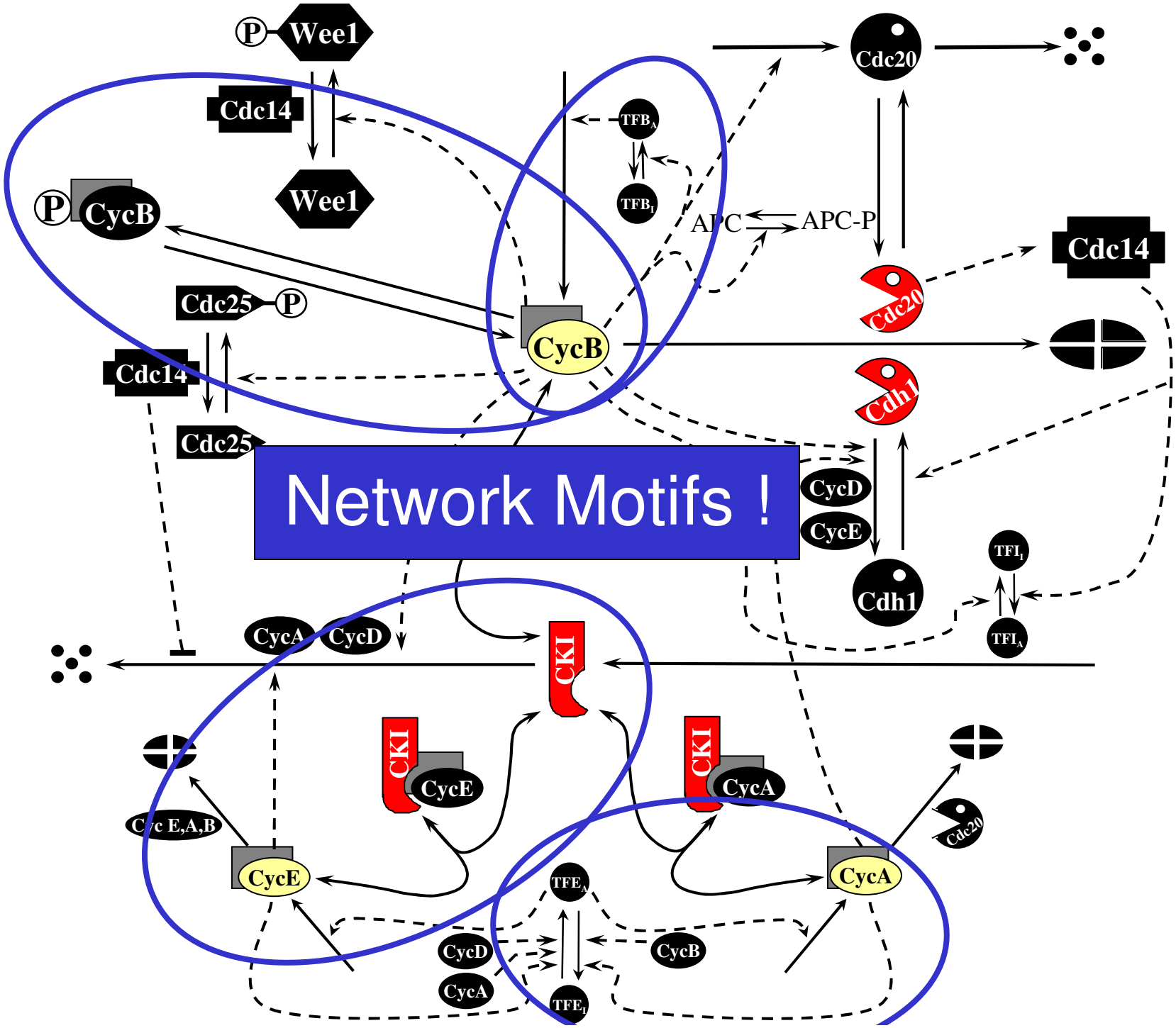
“Machine-readable” form…

$$\frac{\mathrm{d}[\mathrm{CycB}]}{\mathrm{d}t} = \underbrace{k_1 + k_1'[\mathrm{TFB}]}_{\text{synthesis}} - \underbrace{\left(k_2 + k_2'[\mathrm{Cdh1}]\right)[\mathrm{CycB}]}_{\text{degradation}} - \underbrace{k_3[\mathrm{CKI}][\mathrm{CycB}]}_{\text{binding}}$$

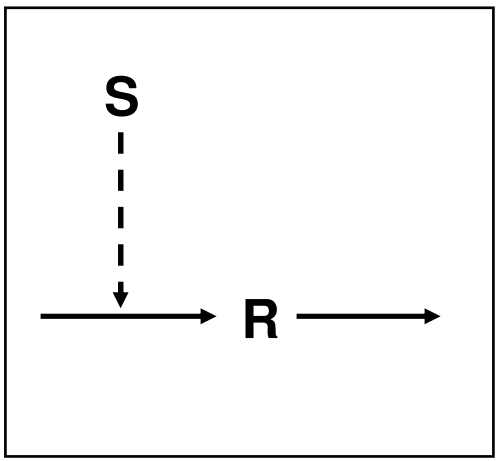
$$\underbrace{-k_4[\mathrm{Wee1}][\mathrm{CycB}]}_{\text{phosphorylation}} + \underbrace{k_5[\mathrm{Cdc25}][\mathrm{CycB{\sim}P}]}_{\text{dephosphorylation}}$$

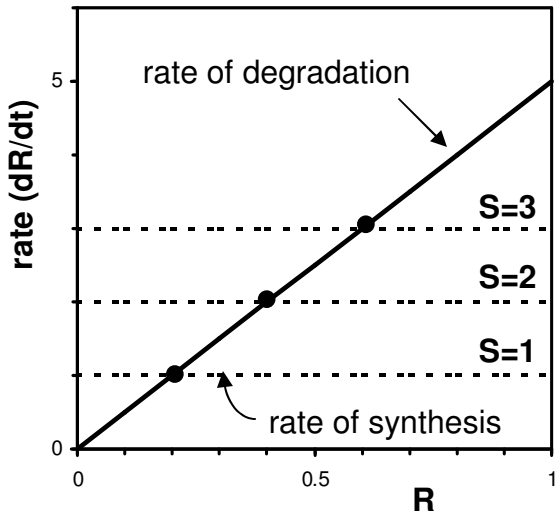
$$\frac{\mathrm{d}[\mathrm{Cdc25}]}{\mathrm{d}t} = \underbrace{\frac{\left(k_6 + k_6'[\mathrm{CycB}]\right)\left([\mathrm{Cdc25}]_\mathrm{T} - [\mathrm{Cdc25}]\right)}{J_6 + [\mathrm{Cdc25}]_\mathrm{T} - [\mathrm{Cdc25}]}}_{\text{activation}} - \underbrace{\frac{k_7[\mathrm{PPase}][\mathrm{Cdc25}]}{J_7 + [\mathrm{Cdc25}]}}_{\text{inactivation}}$$

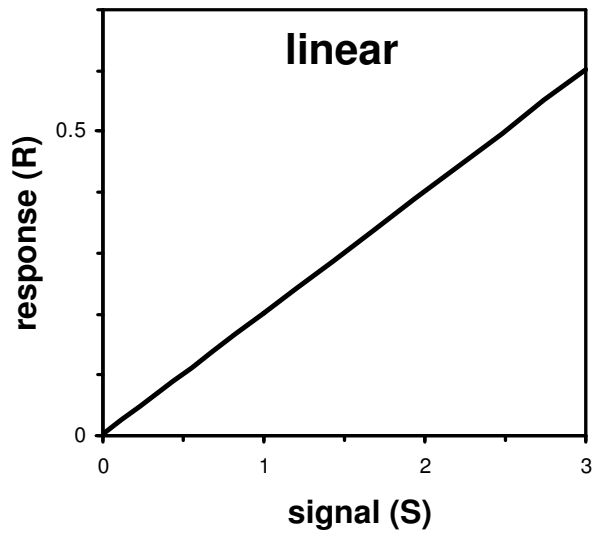

S
G2
M
G1
S
G2
M
G1
S
mass/nucleus
P-Cdk1
CycB
Cdk1
CycB
CKI
Cdh1
Cdc20
Wee1
Cdc25
0
50
100
M-phase
G1
G2
S-phase


Network Motifs !
Wee1
Cdc14
Wee1
CycB
Cdc25
Cdc14
Cdc25
CycB
TFB_A
TFB_I
APC
APC-P
Cdc20
Cdc20
Cdc14
Cdh1
CycD
CycE
Cdh1
TFI_I
TFI_A
CycA
CycD
CKI
CKI
CycE
CKI
CycA
Cyc E,A,B
CycE
CycA
Cdc20
TFE_A
CycD
CycA
CycB
TFE_I

Gene Expression



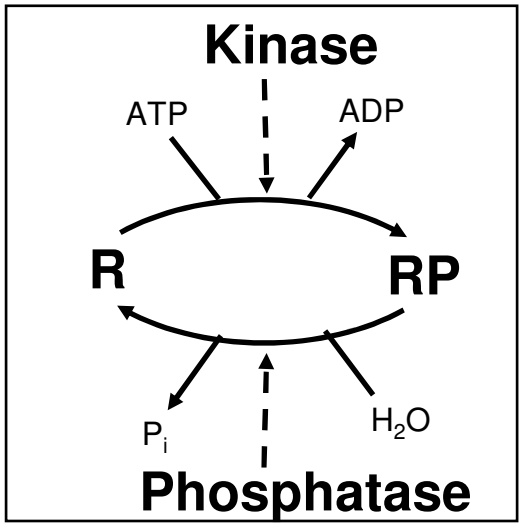


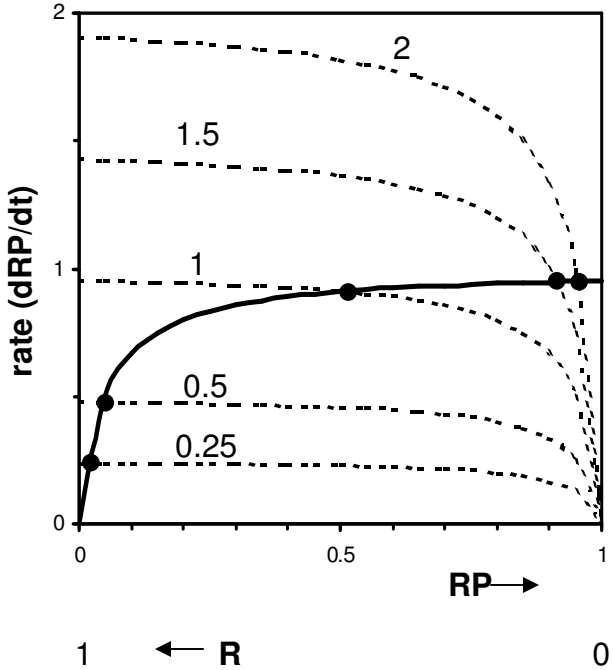


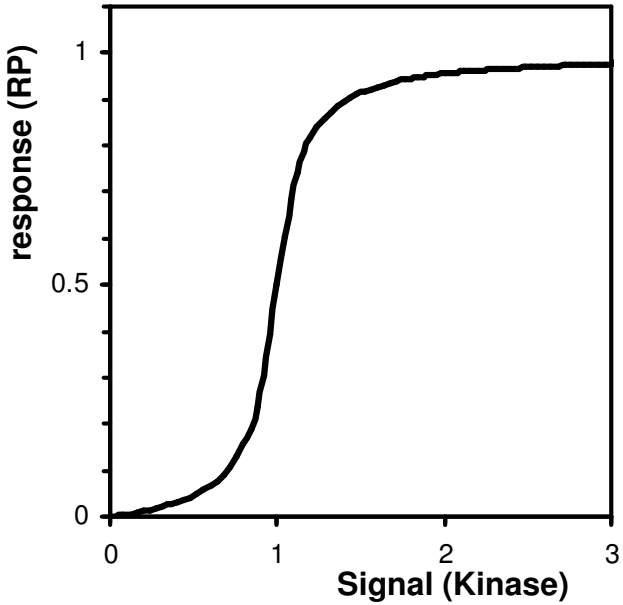
$$\frac{\mathrm{d}R}{\mathrm{d}t} = k_1 S - k_2 R, \quad R_{\mathrm{ss}} = \frac{k_1 S}{k_2}$$

Signal-Response Curve

Protein Phosphorylation



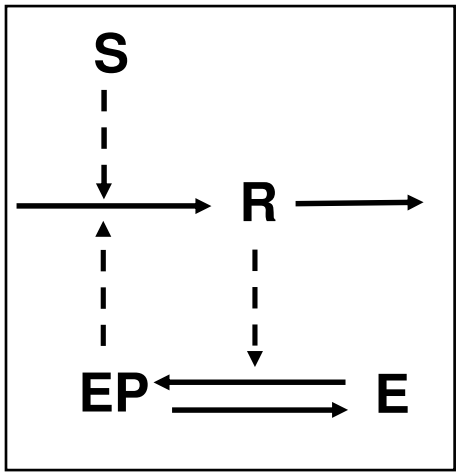


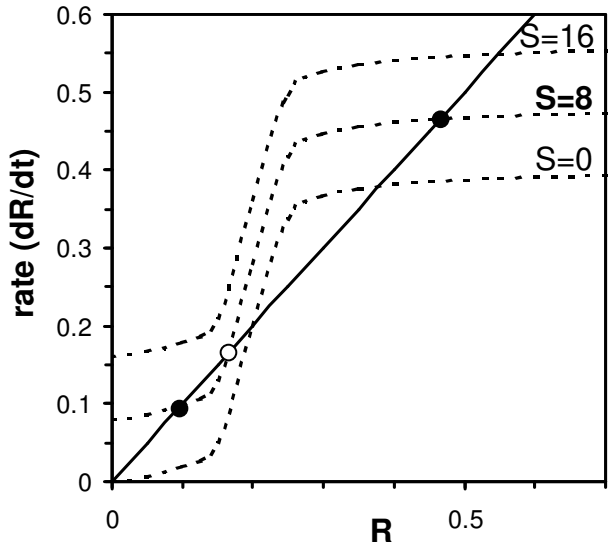


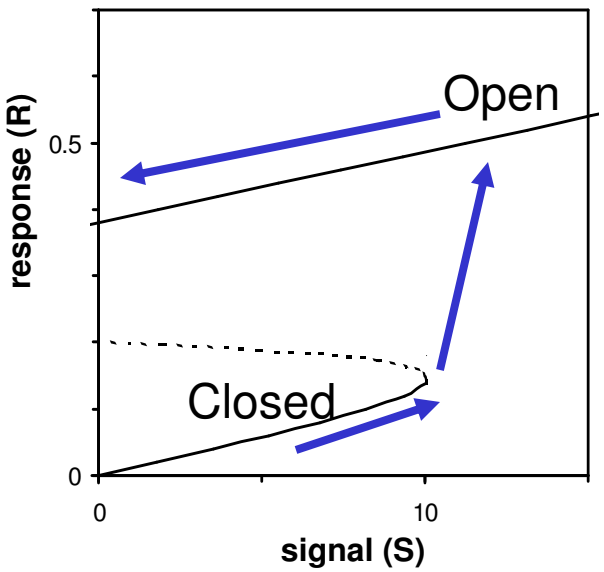
"Buzzer"

Goldbeter & Koshland, 1981

Protein Synthesis: Positive Feedback





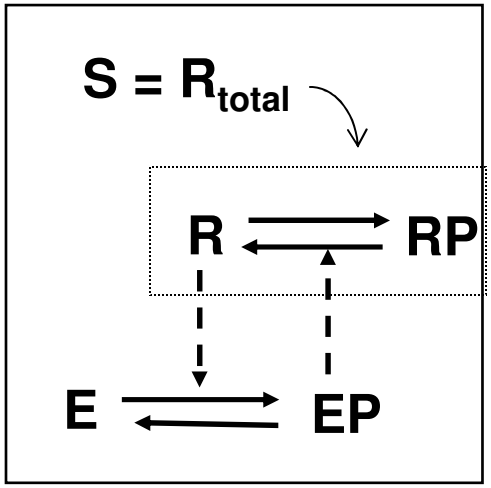


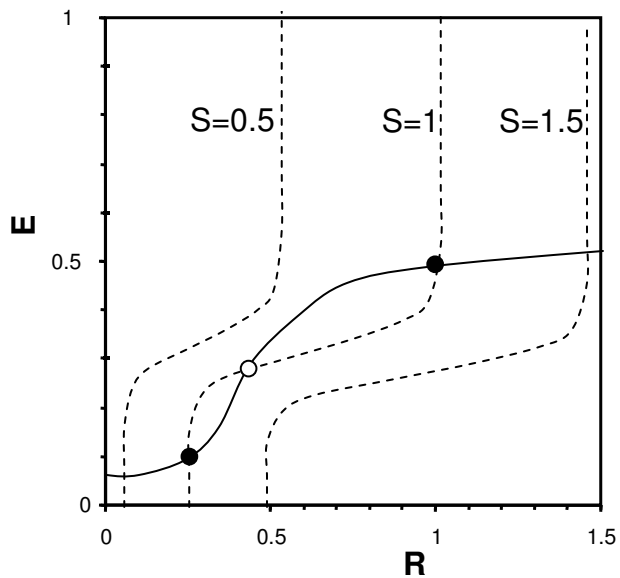
Bistability

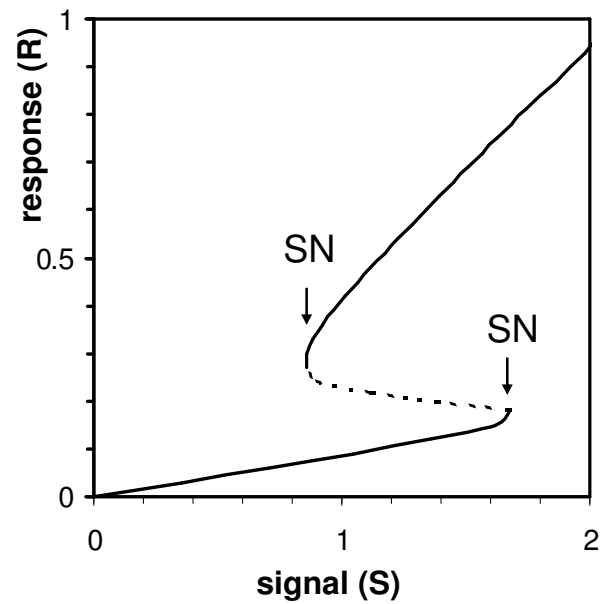
"Fuse"

Griffith, 1968

Coupled Buzzers

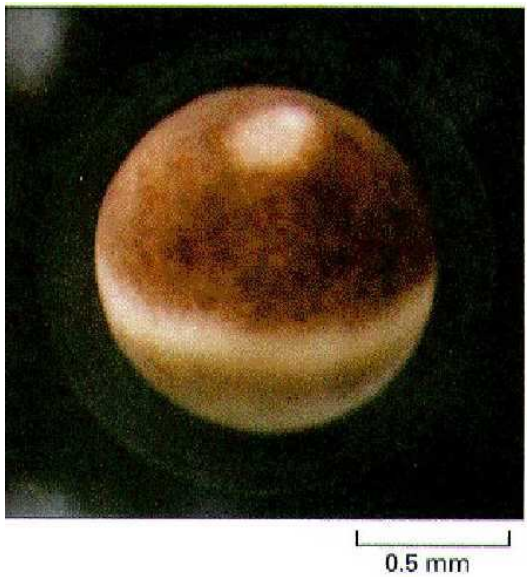




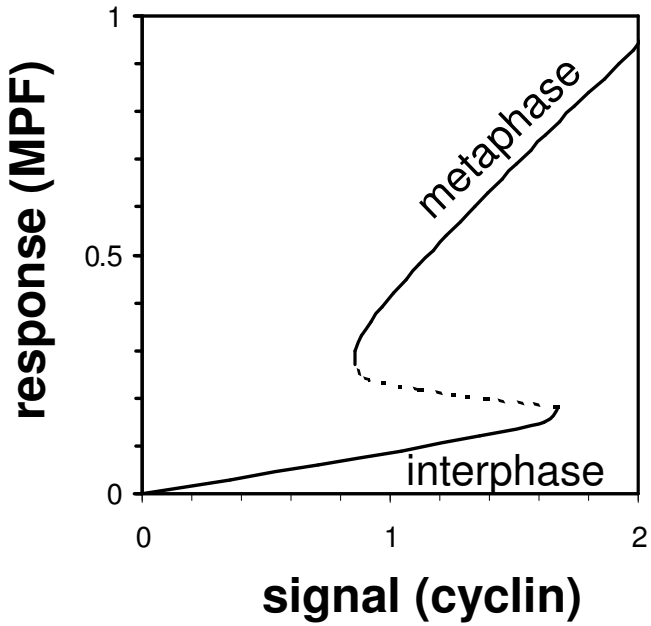


Bistability

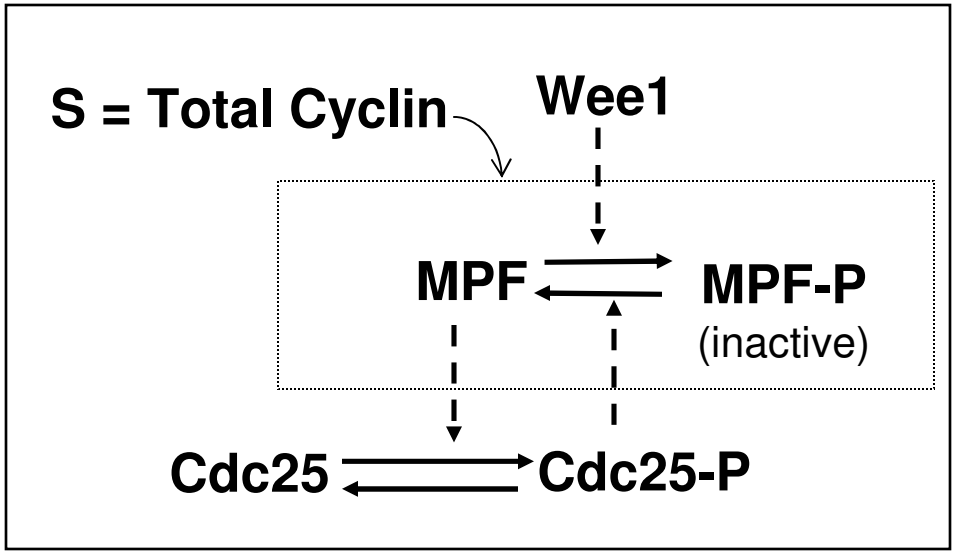
“Toggle”


0.5 mm

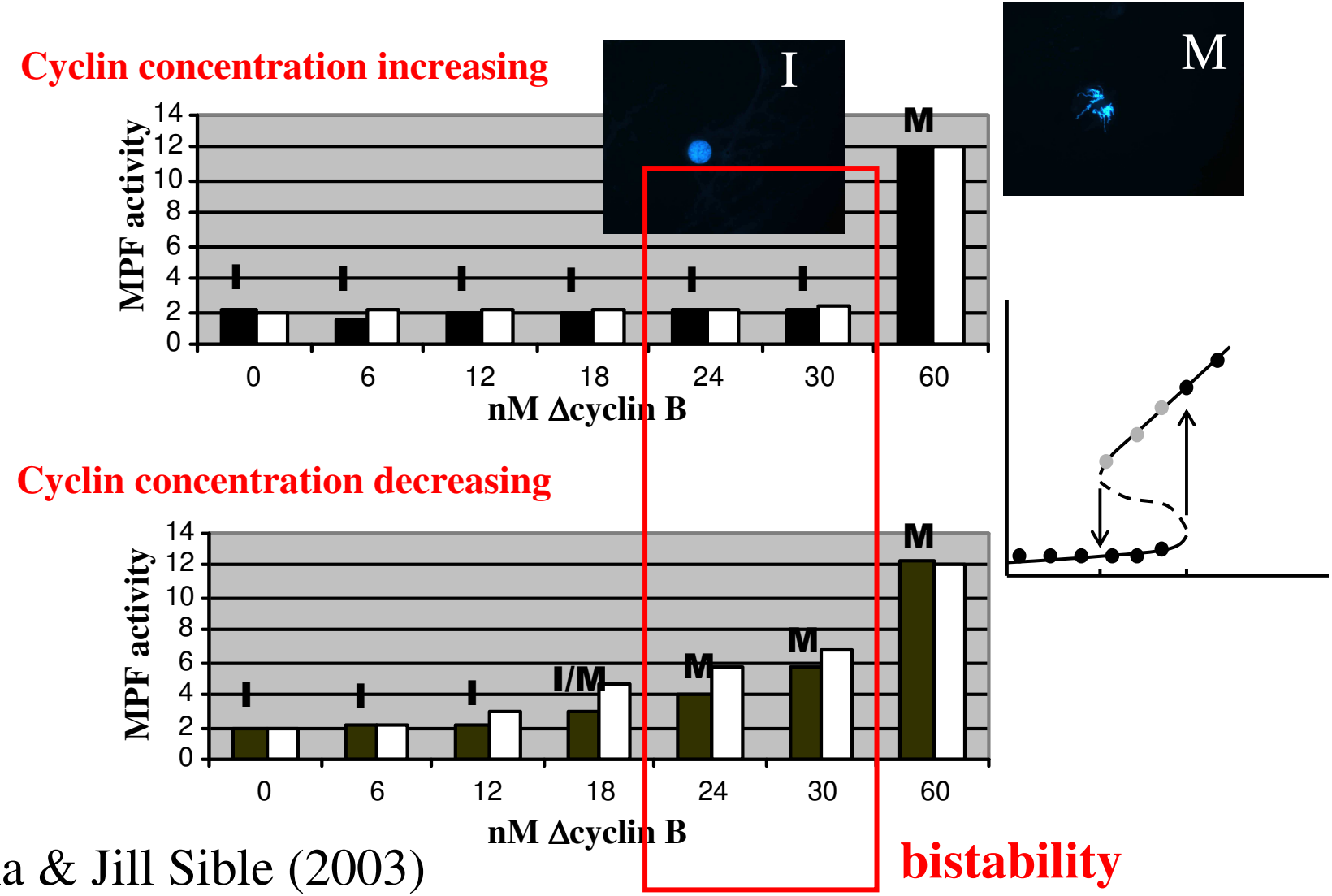
Frog egg


1
0.5
0
0
1
2
response (MPF)
signal (cyclin)
metaphase
interphase

MPF = 
CycB

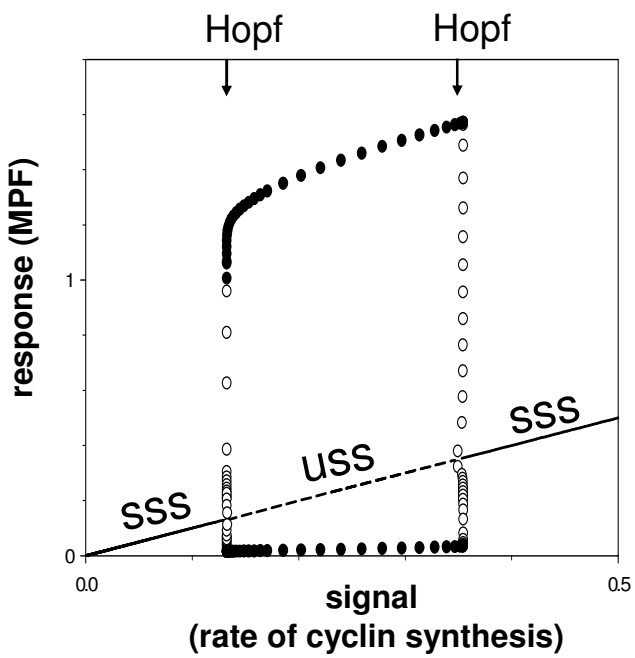

S = Total Cyclin
Wee1
MPF
MPF-P
(inactive)
Cdc25
Cdc25-P

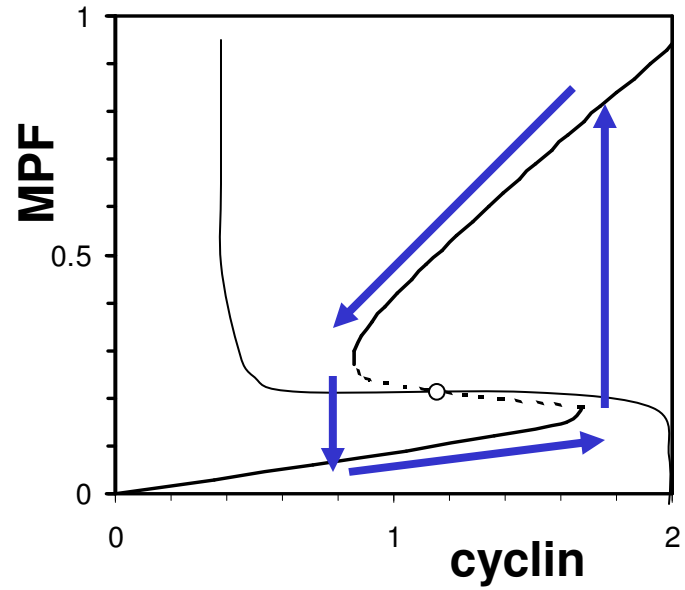
MPF activity depends on total cyclin concentration and on the history of the extract

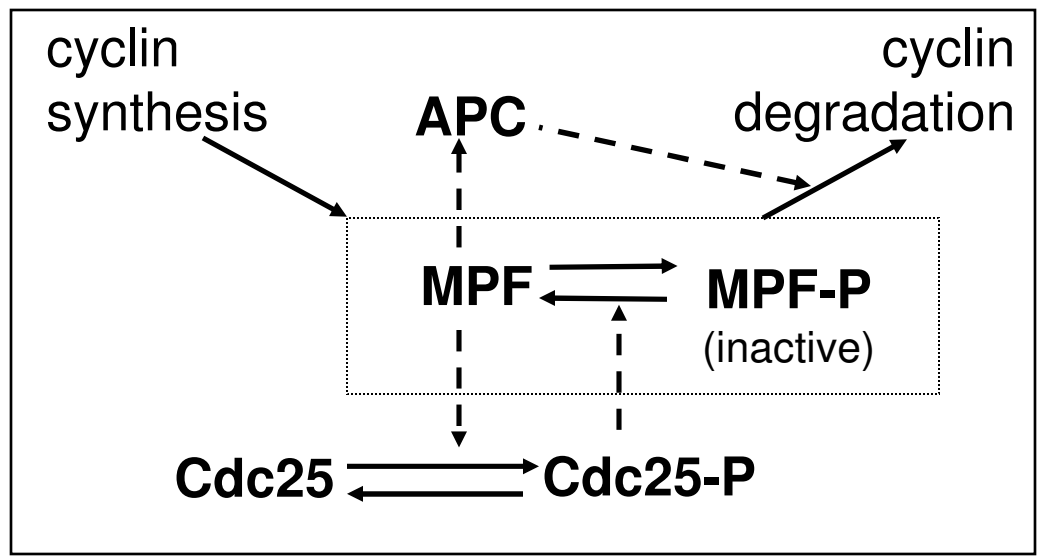


Wei Sha & Jill Sible (2003)

Oscillations







Pomerening, Kim & Ferrell
Cell (2005)

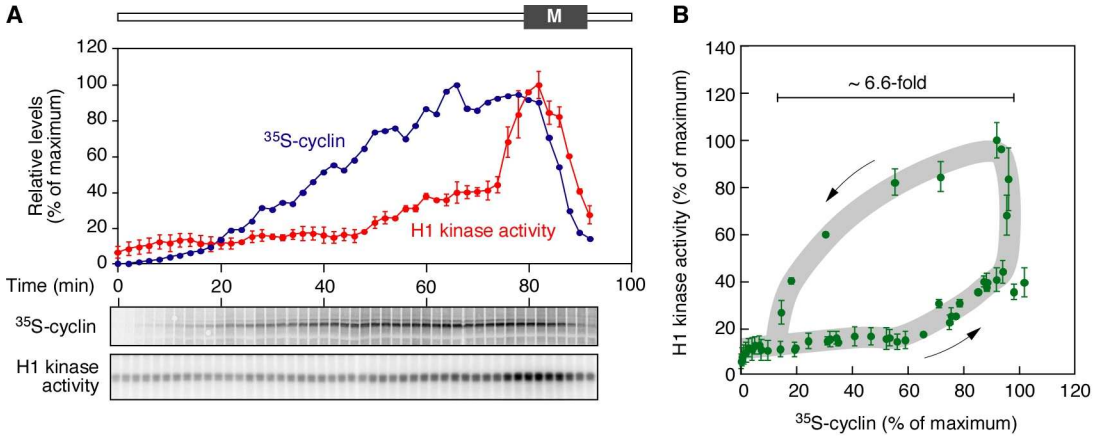
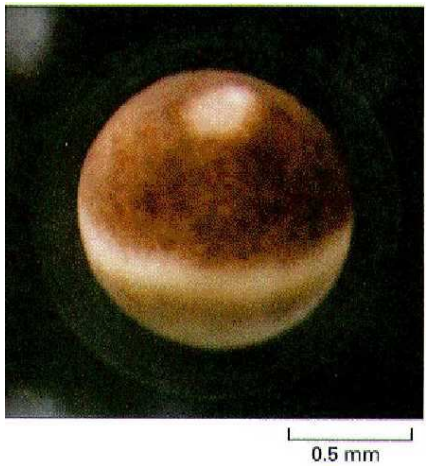


Figure 3
Pomerening, Kim and Ferrell



If knock-out positive feedback loop, then oscillations become faster and smaller amplitude…

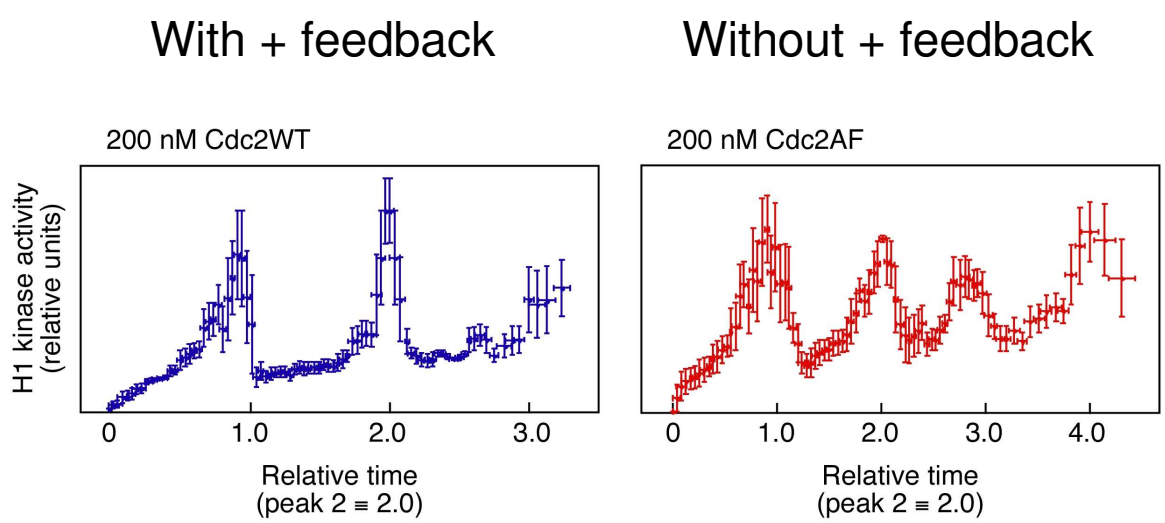
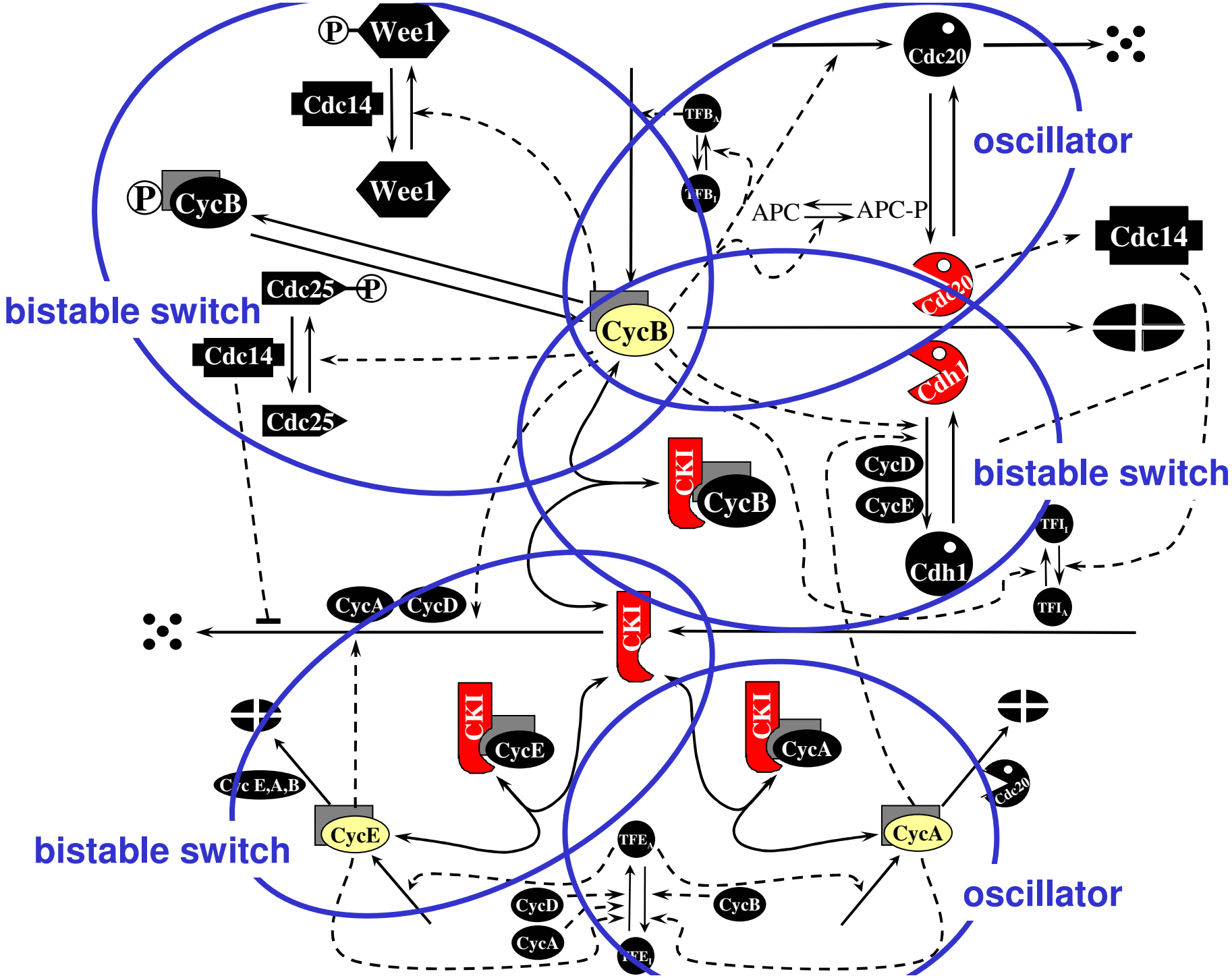
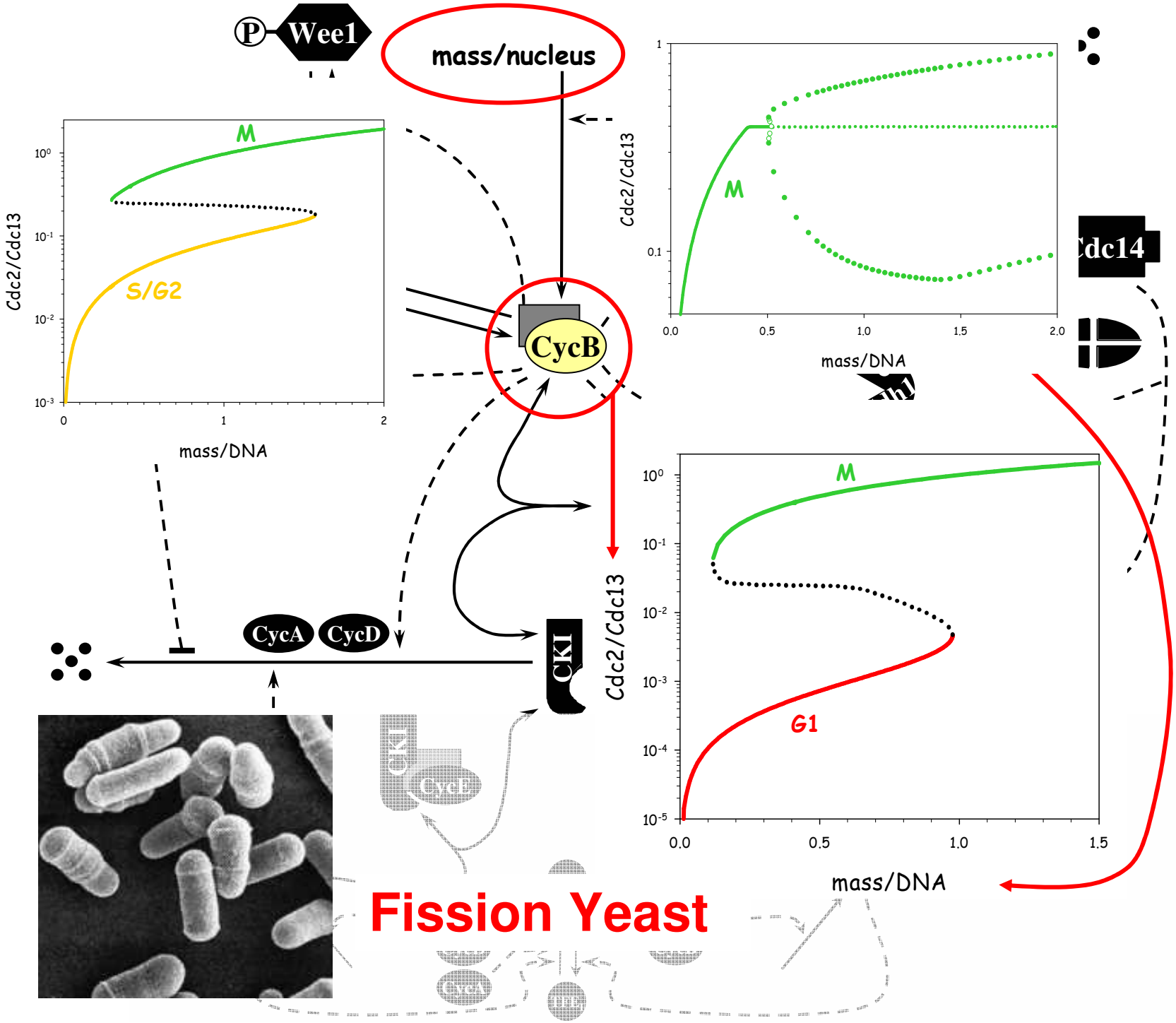
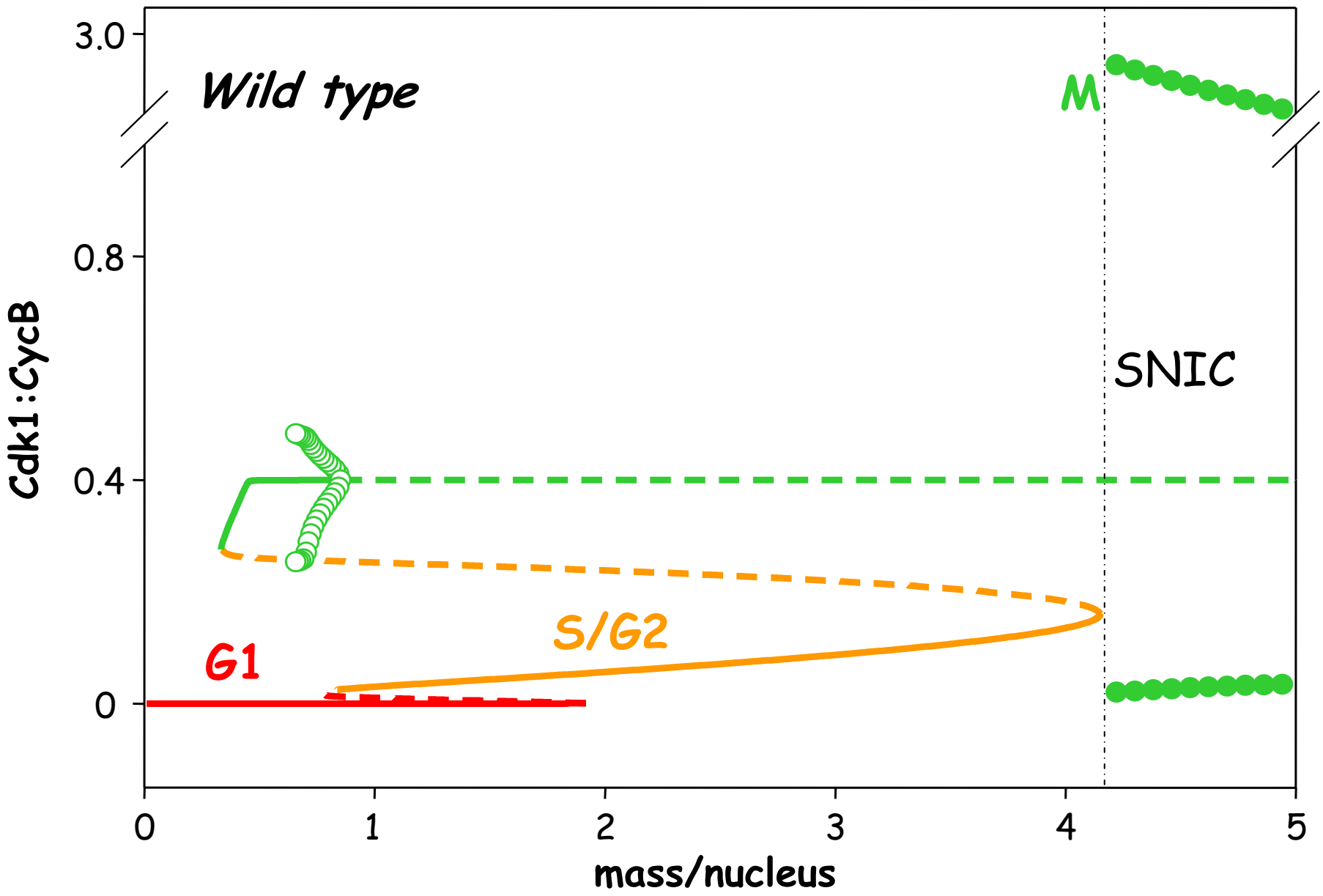


Figure 4. Pomerening, Kim and Ferrell

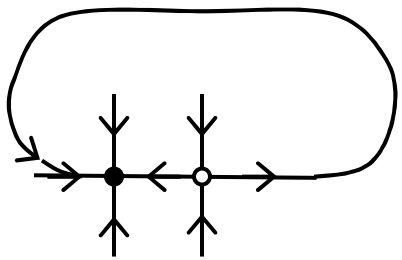

Wee1
Cdc14
Wee1
CycB
Cdc25
Cdc14
Cdc25
bistable switch
Cdc20
oscillator
APC
APC-P
Cdc14
Cdc20
CycB
Cdh1
CKI
CycB
CycD
CycE
bistable switch
Cdh1
CycA
CycD
CKI
CKI
CycE
CKI
CycA
Cyc E,A,B
CycE
CycA
Cdc20
bistable switch
CycD
CycA
CycB
oscillator


P
Wee1
mass/nucleus
M
S/G2
Cdc2/Cdc13
mass/DNA
CycB
Cdc2/Cdc13
M
mass/DNA
Cdc14
CycA
CycD
CKI
M
G1
Cdc2/Cdc13
mass/DNA
Fission Yeast

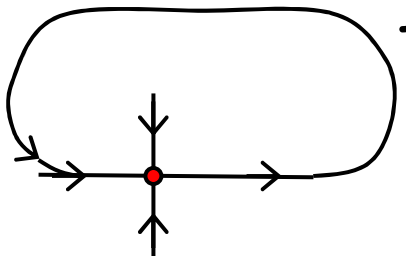

Wild type
M
SNIC
S/G2
G1
3.0
0.8
0.4
0
Cdk1:CycB
0
1
2
3
4
5
mass/nucleus

SNIC Bifurcation

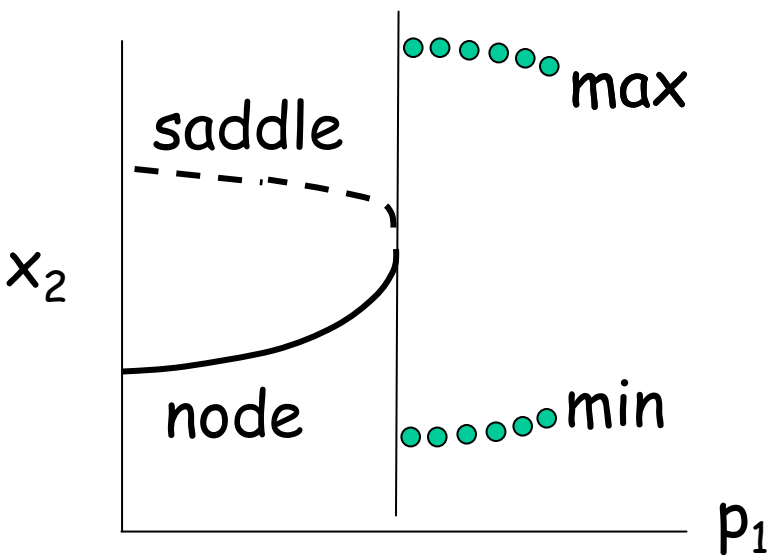
Invariant Circle



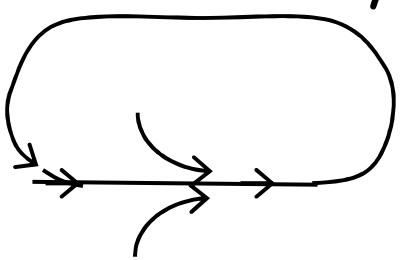
Saddle-Node on an Invariant Circle

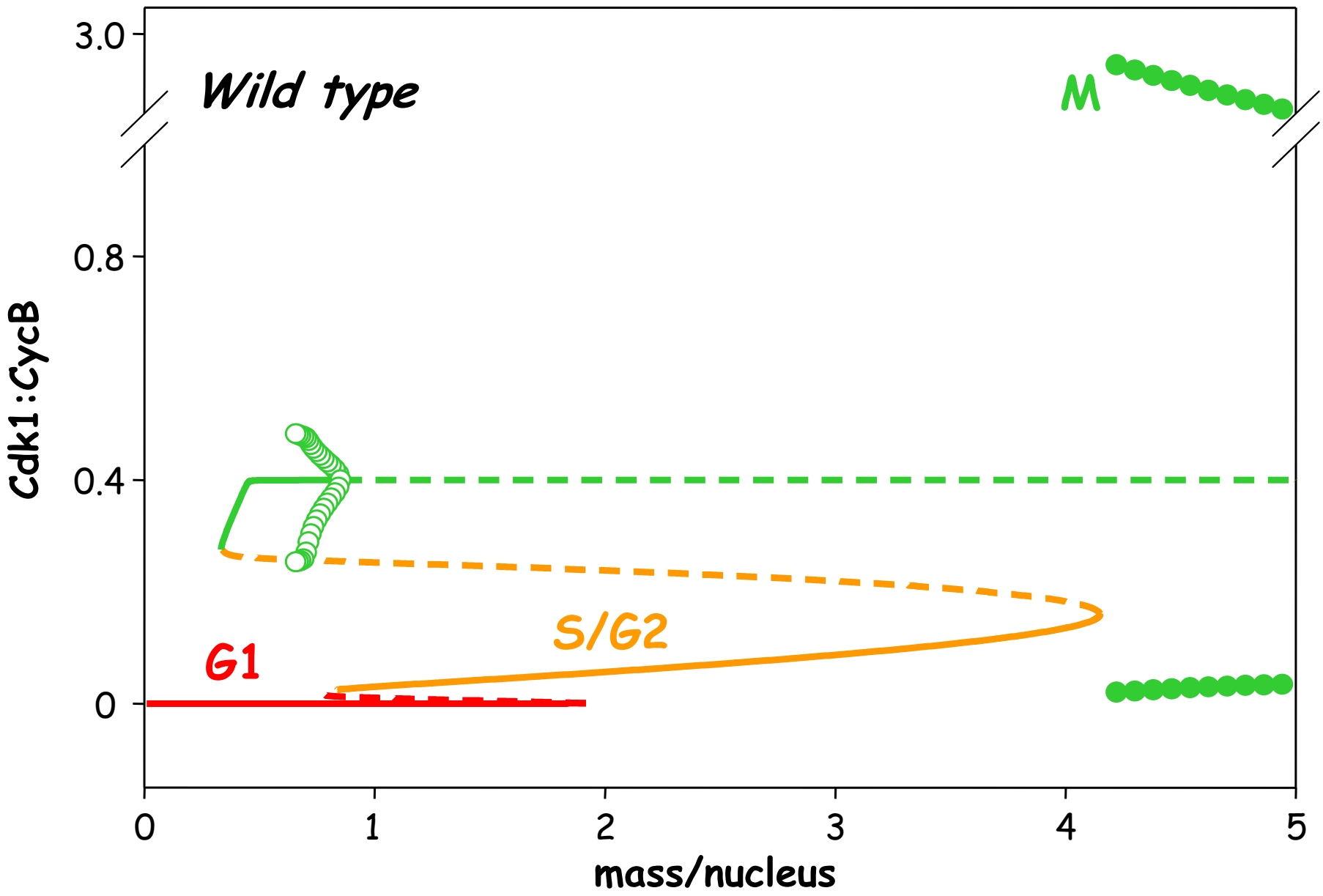


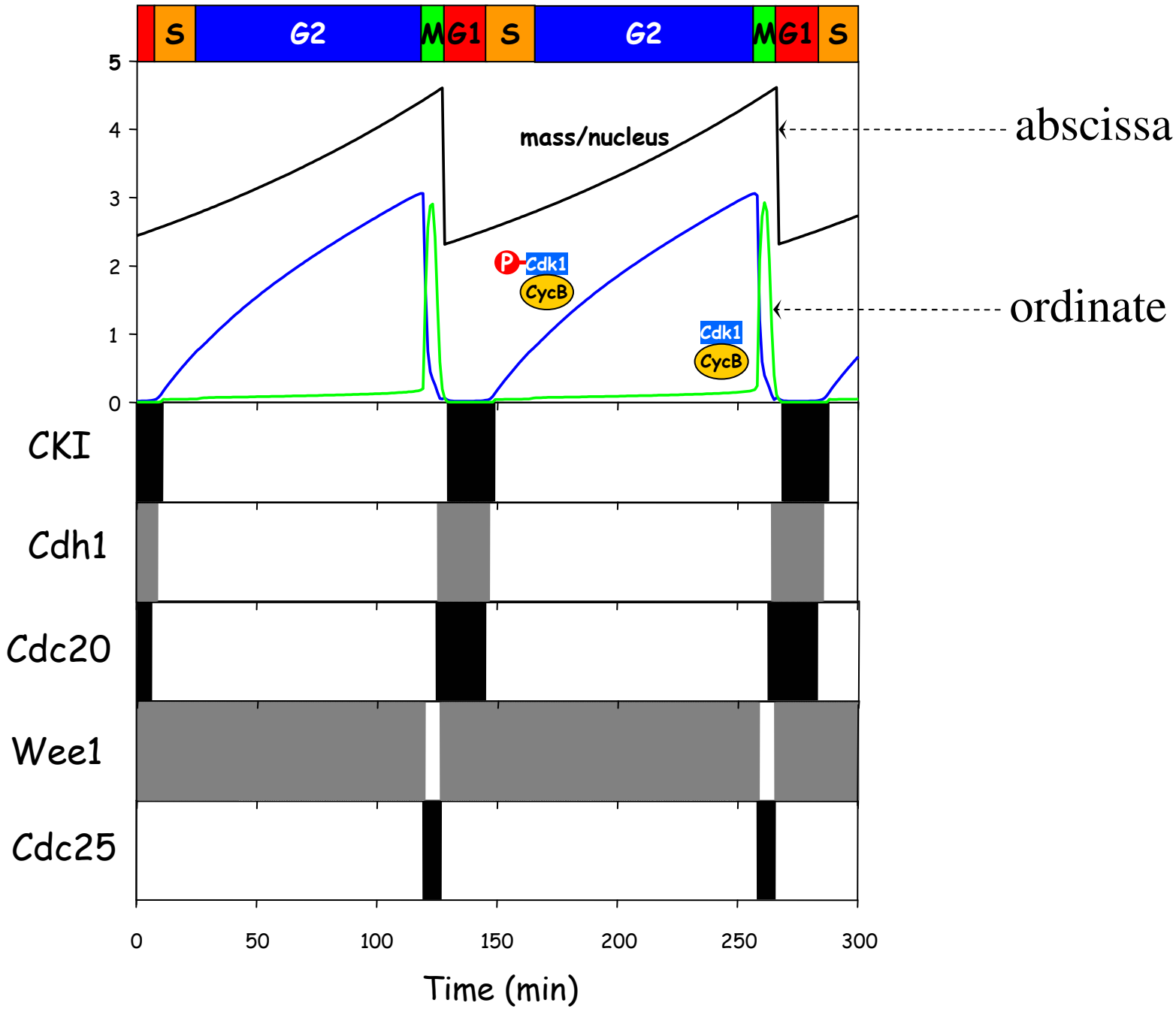
SNIC

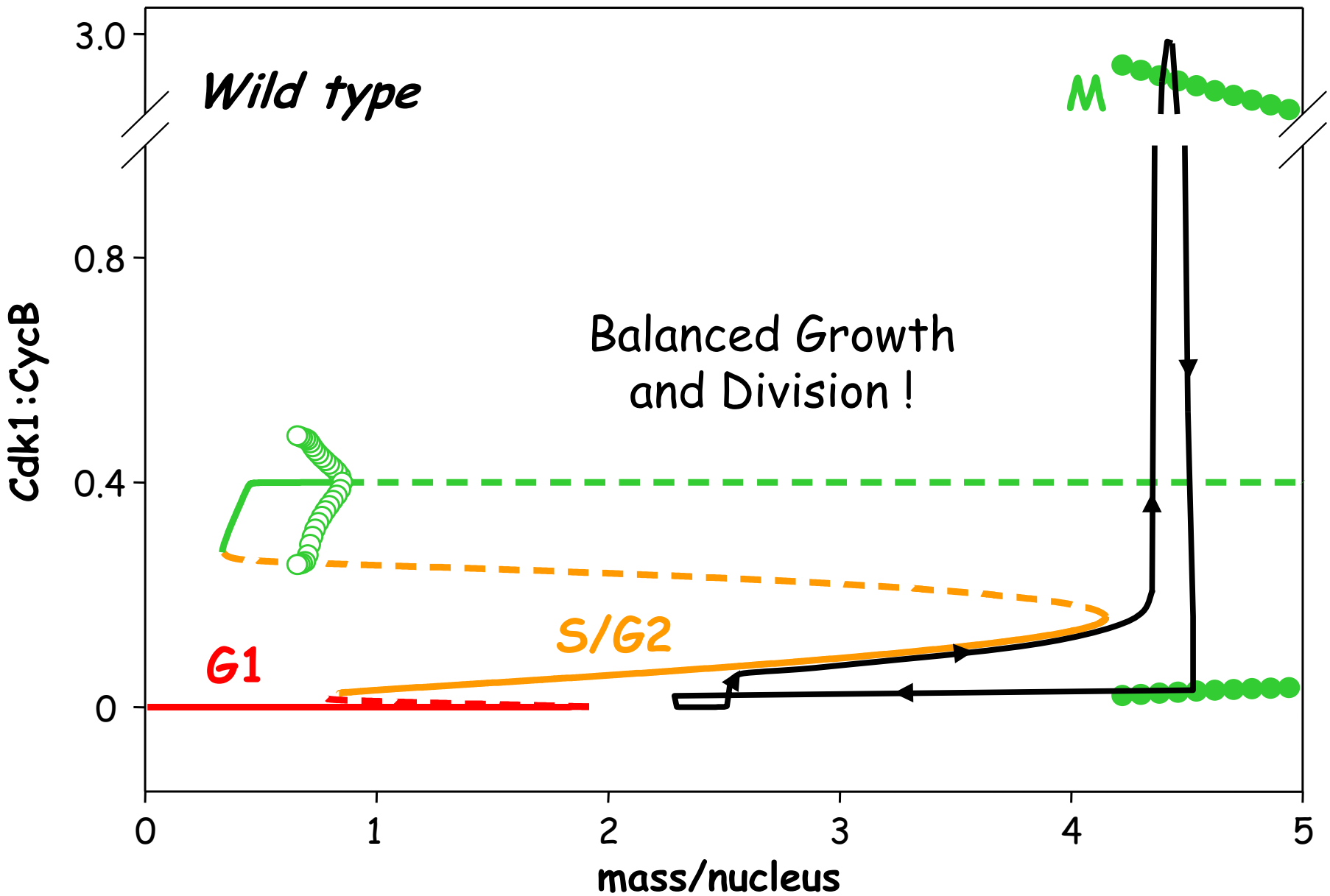


Limit Cycle




Wild type
M
S/G2
G1
3.0
0.8
0.4
0
Cdk1:CycB
0
1
2
3
4
5
mass/nucleus

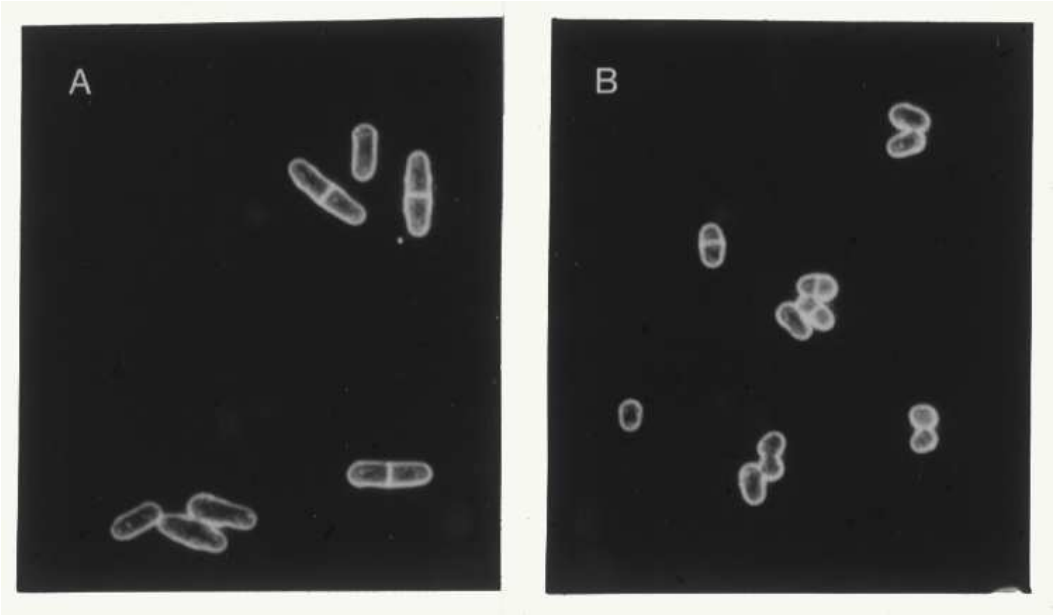

S
G2
M
G1
S
G2
M
G1
S
5
4
3
2
1
0
mass/nucleus
P-Cdk1
CycB
Cdk1
CycB
abscissa
ordinate
CKI
Cdh1
Cdc20
Wee1
Cdc25
0
50
100
150
200
250
300
Time (min)


Wild type
M
Balanced Growth
and Division !
S/G2
G1
3.0
0.8
0.4
0
Cdk1:CycB
0
1
2
3
4
5
mass/nucleus

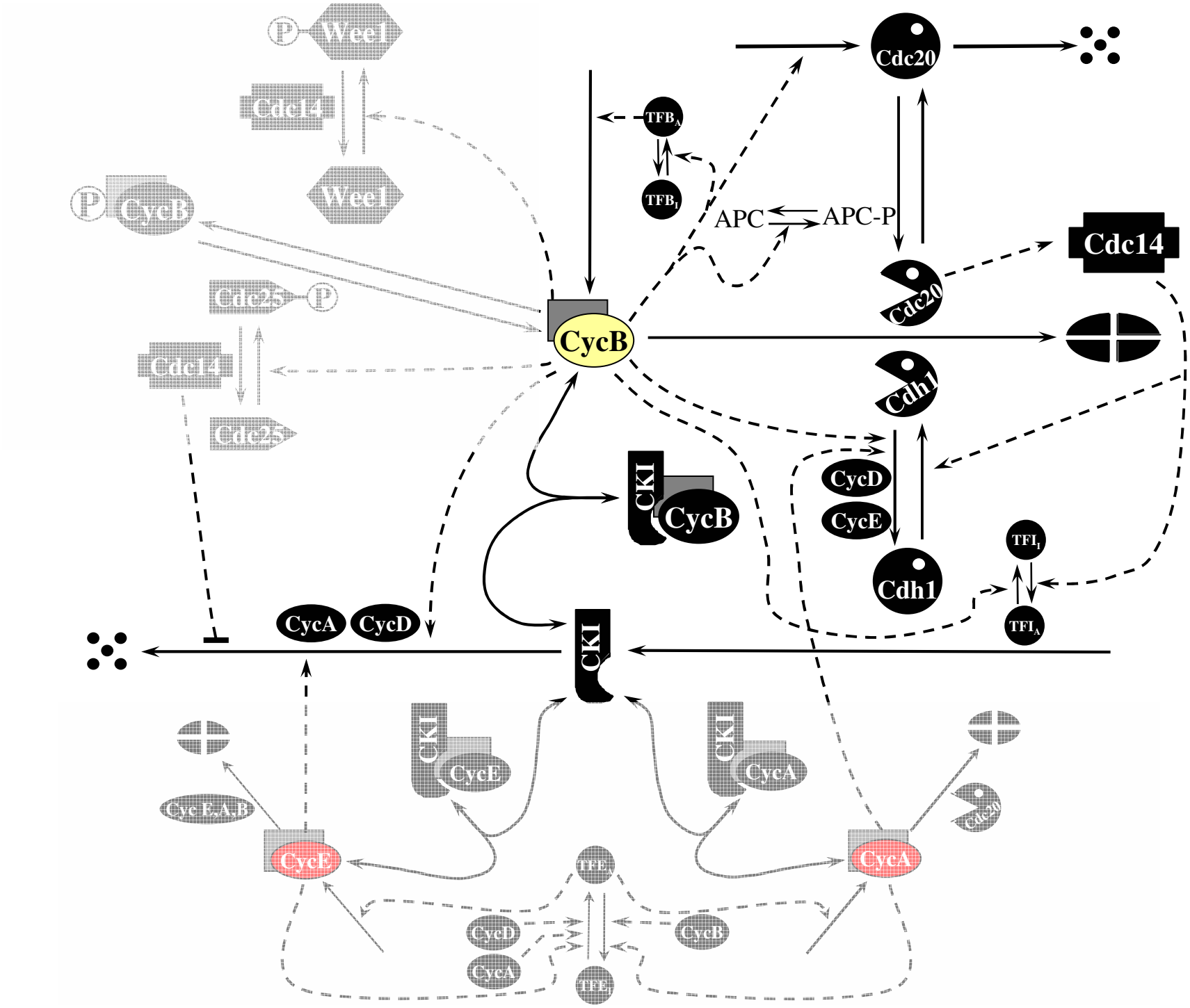
Nature, Vol, 256, No. 5518, pp. 547-551, August 14, 1975

Genetic control of cell size at cell division in yeast

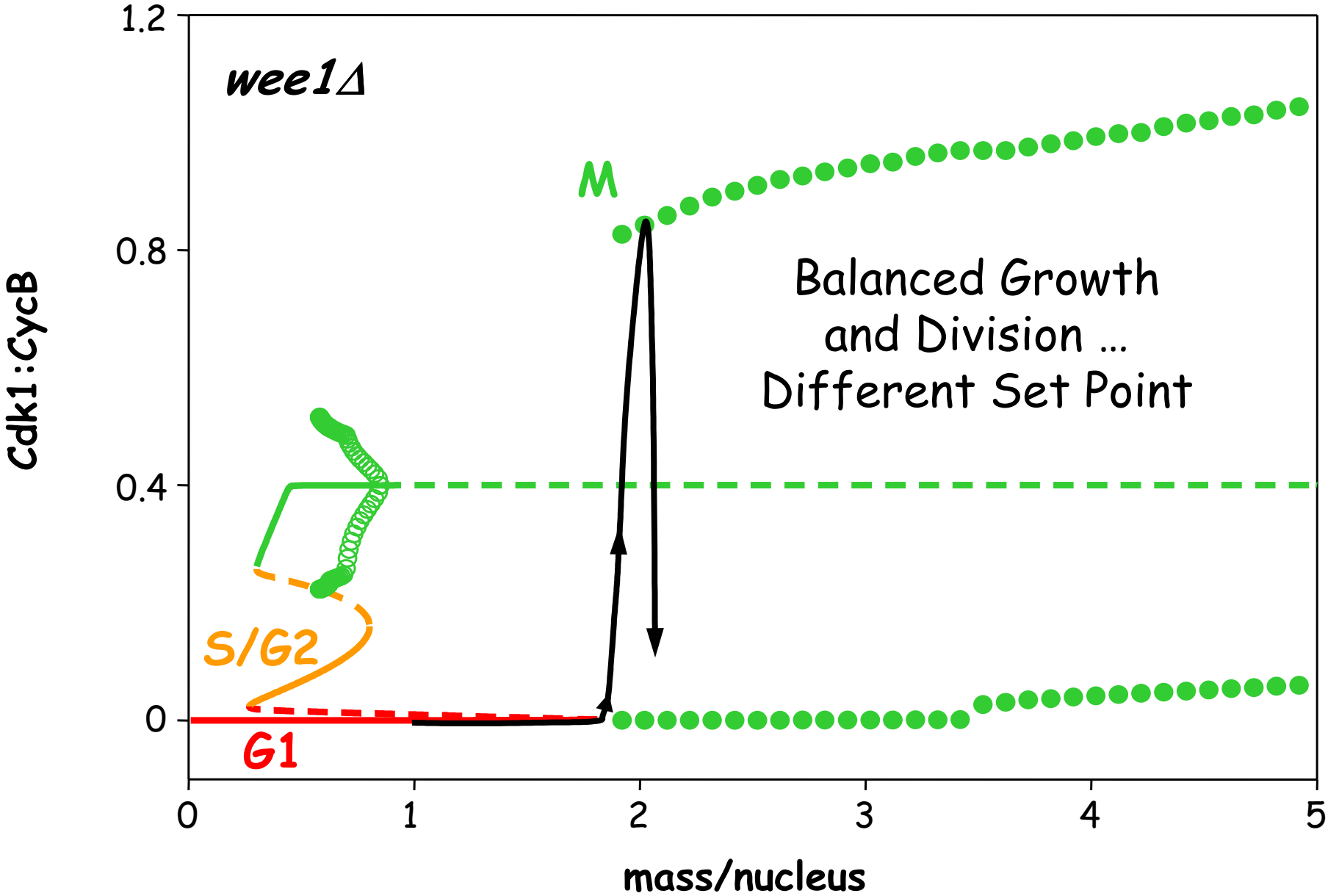
Paul Nurse
Department of Zoology, West Mains Road, Edinburgh EH9 3JT, UK

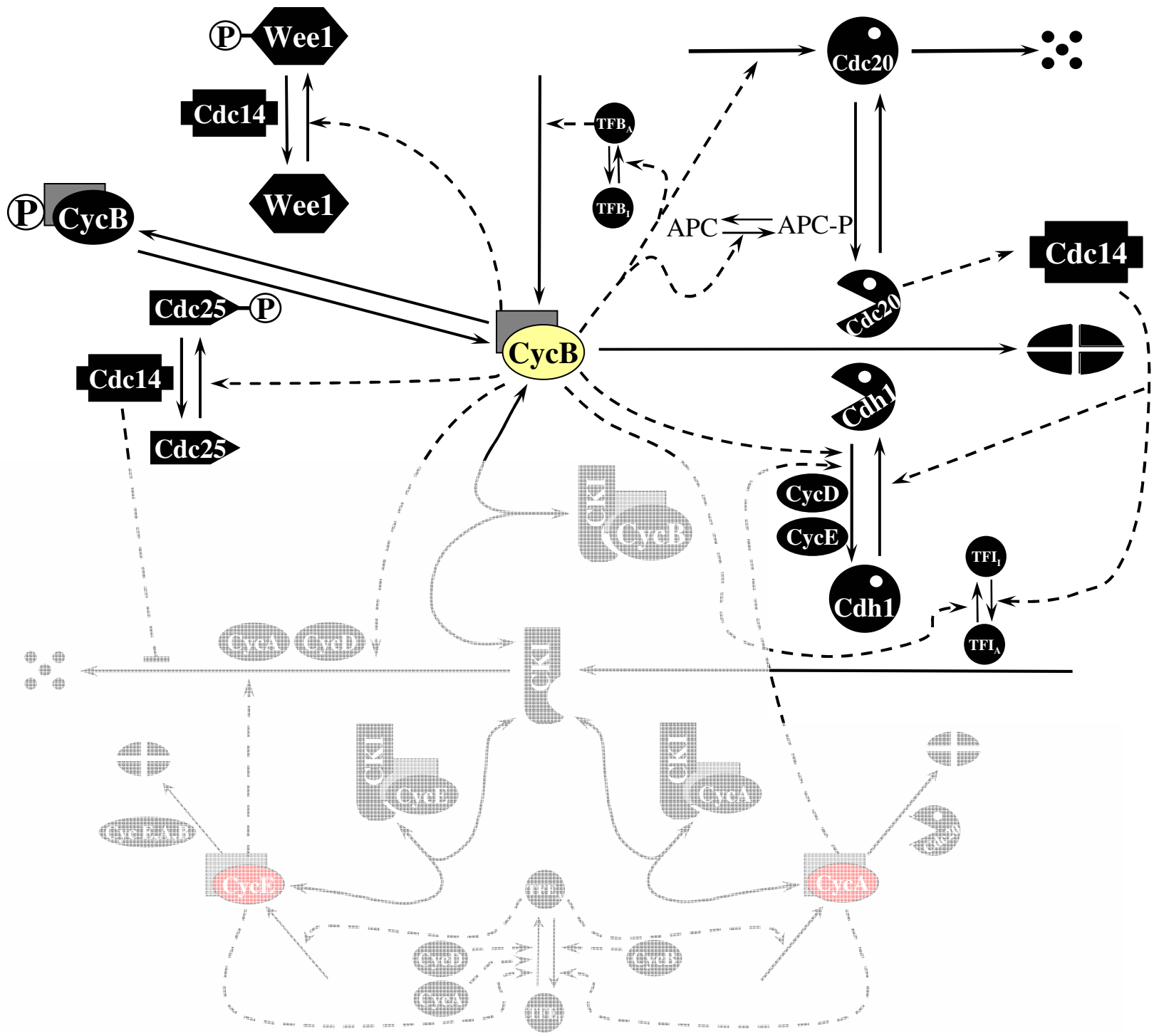


wild-type ***wee1Δ***

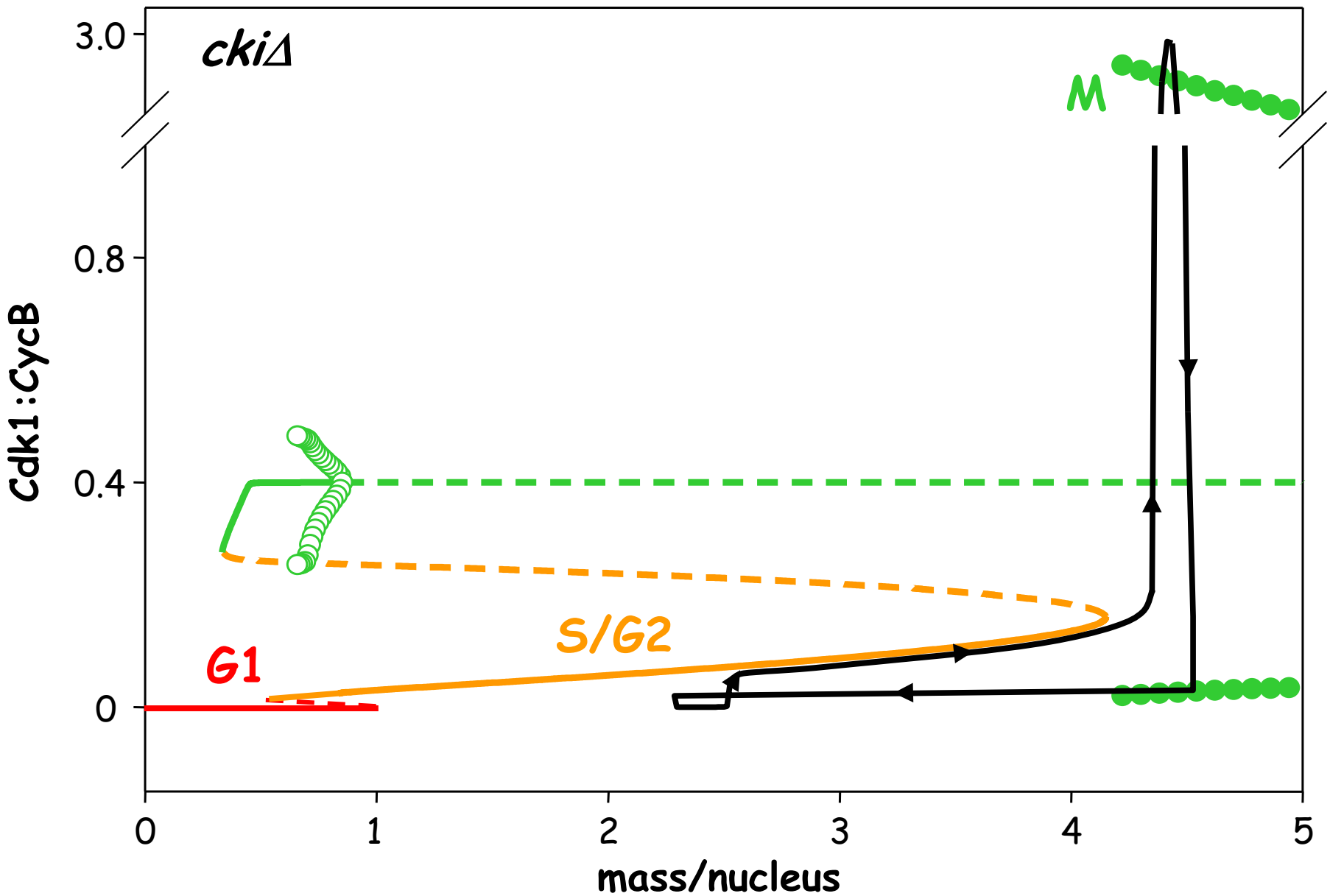

P
Wee1
Cdc14
Wee1
P
CycB
Cdc25
P
Cdc14
Cdc25
Cdc20
TFB$_A$
TFB$_I$
APC
APC-P
Cdc14
Cdc20
CycB
Cdh1
CKI
CycB
CycD
CycE
Cdh1
TFI$_I$
TFI$_A$
CycA
CycD
CKI
CycE
CycA
Cyc E A B
CycE
CycA
TFB$_I$
CycD
CycA
CycB
TFB$_A$

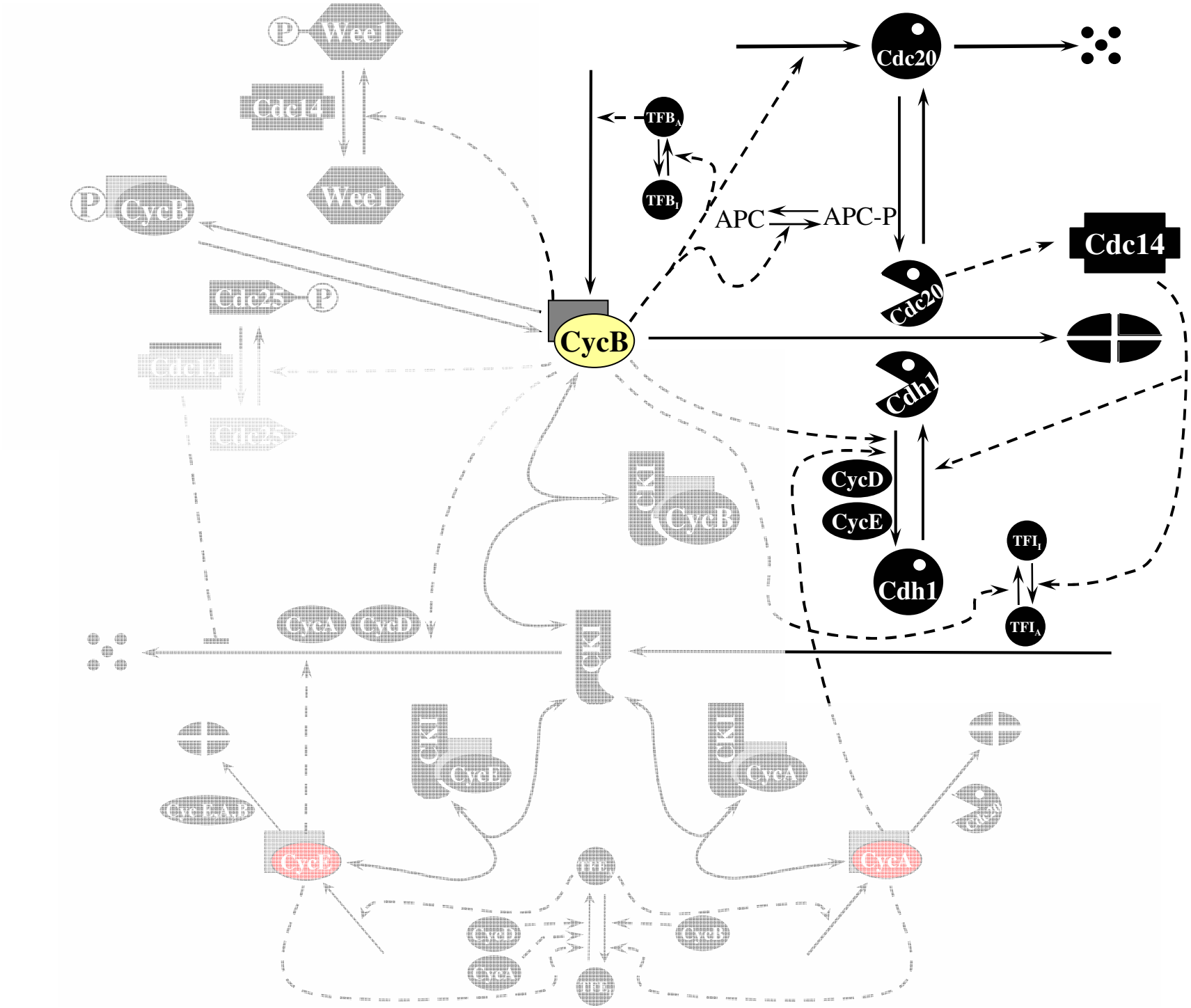
wee1Δ cells are about one-half the size of wild type



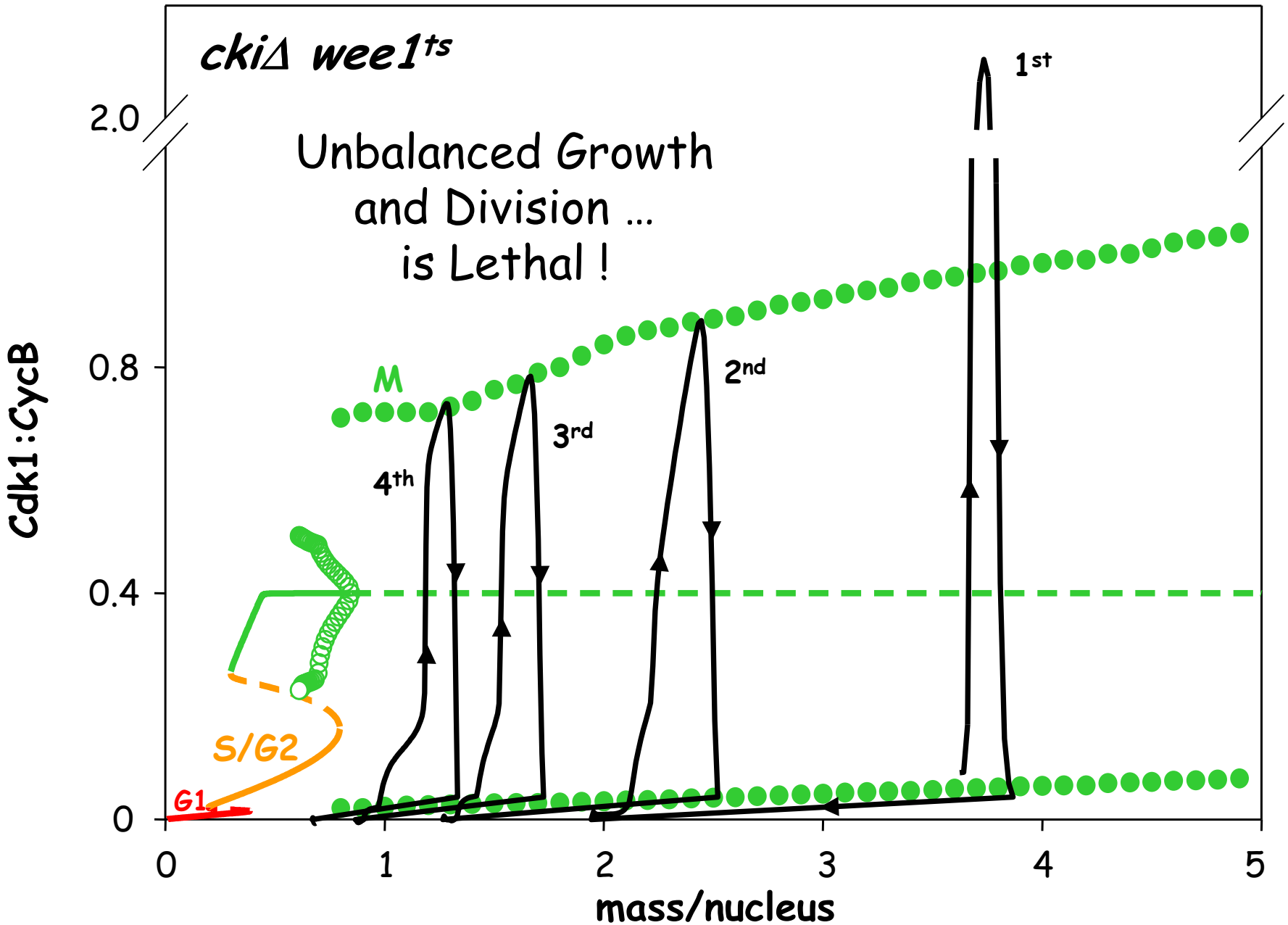

P
Wee1
Cdc14
Wee1
P
CycB
Cdc25
P
Cdc14
Cdc25
CycB
TFB$_A$
TFB$_I$
APC
APC-P
Cdc20
Cdc20
Cdc14
Cdh1
CycD
CycE
Cdh1
TFI$_I$
TFI$_A$

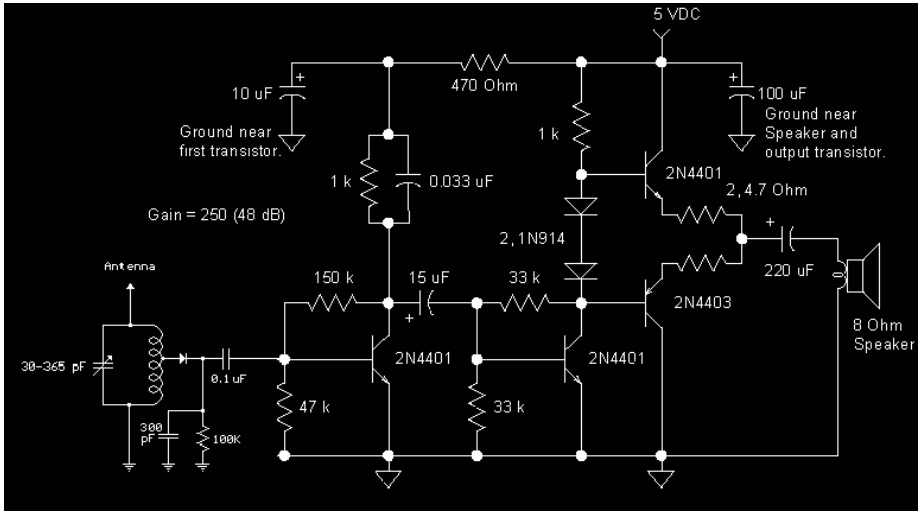
The Start module is not required during mitotic cycles

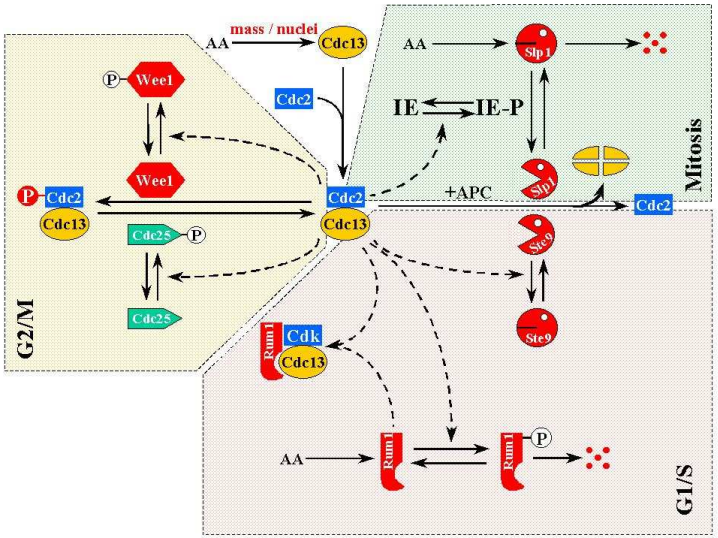


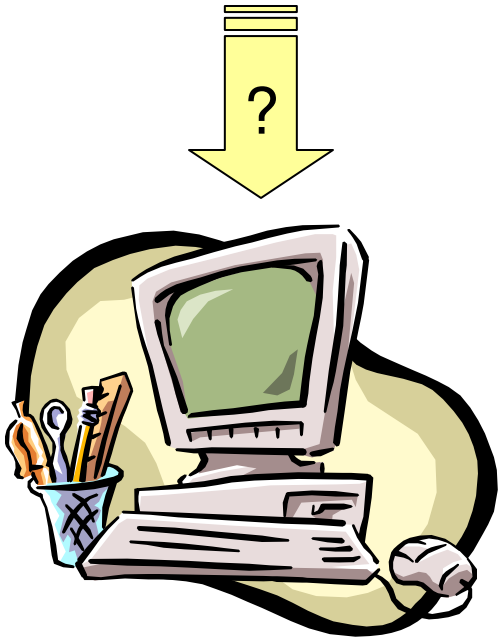

Cdc20
TFB$_A$
TFB$_I$
APC
APC-P
Cdc14
Cdc20
CycB
Cdh1
CycD
CycE
Cdh1
TFI$_I$
TFI$_A$
Wee1
Cdc14
Wee1
CycB
Cdc25
P
Cdc25
Cdc25
CycB
CycA
CycD
CycB
CycA
CycB
CycA
CycD
CycB
CycD
CycA

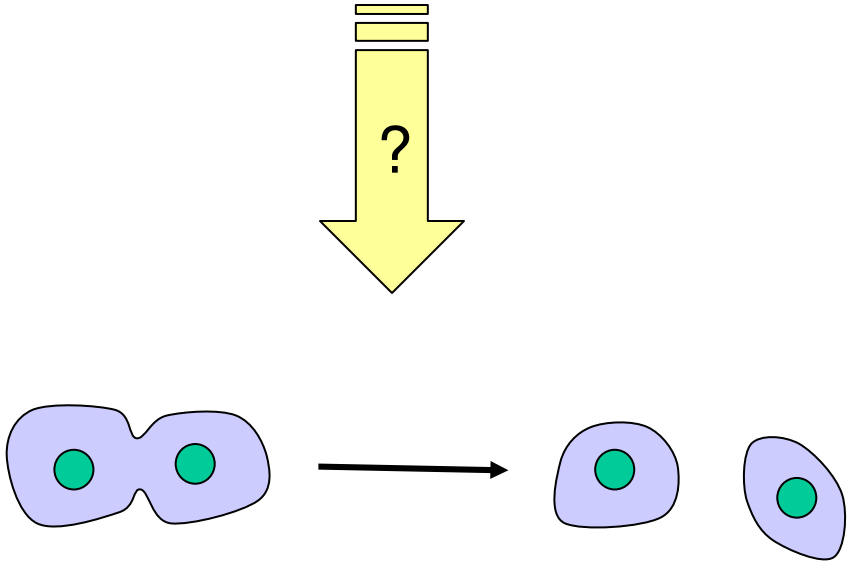
Cells become progressively smaller without size control




5 VDC
10 uF
470 Ohm
100 uF
Ground near first transistor.
Ground near Speaker and output transistor.
1 k
1 k
0.033 uF
2N4401
2,4.7 Ohm
Gain = 250 (48 dB)
2,1N914
Antenna
150 k
15 uF
33 k
220 uF
2N4403
8 Ohm Speaker
30-365 pF
0.1 uF
2N4401
2N4401
47 k
33 k
300 pF
100K


mass / nuclei
AA
Cdc13
Wee1
Cdc2
Cdc13
Cdc25
P
Rum1
Cdk
Cdc13
G2/M
AA
Slp1
IE
IE-P
+APC
Cdc2
Mitosis
Ste9
AA
Rum1
Rum1
P
G1/S


?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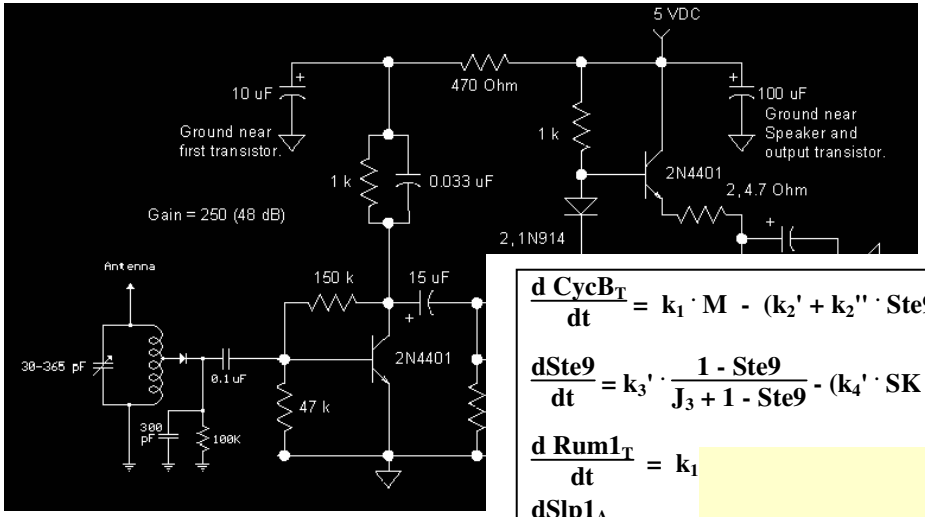


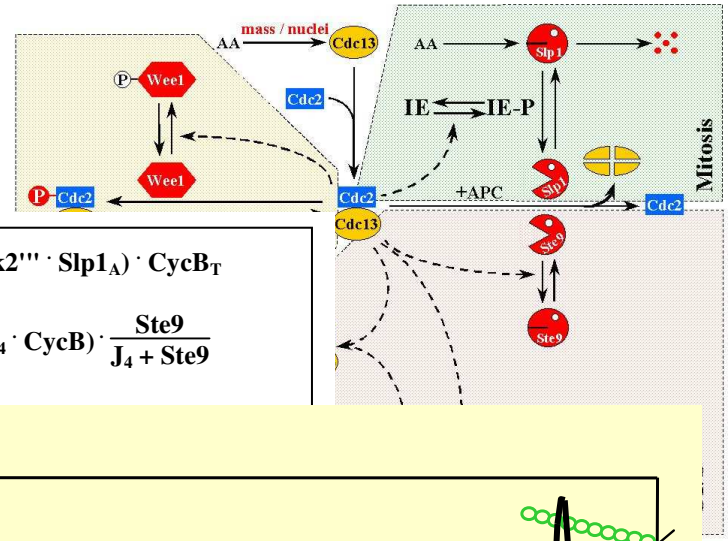
$$\frac{d\,CycB_T}{dt} = k_1 \cdot M - (k_2' + k_2'' \cdot Ste9 + k2''' \cdot Slp1_A) \cdot CycB_T$$

$$\frac{dSte9}{dt} = k_3' \cdot \frac{1 - Ste9}{J_3 + 1 - Ste9} - (k_4' \cdot SK + k_4 \cdot CycB) \cdot \frac{Ste9}{J_4 + Ste9}$$

$$\frac{d\,Rum1_T}{dt} = k_1$$

$$\frac{dSlp1_A}{dt} = k_7 \cdot IE$$

$$\frac{dM}{dt} = \mu \cdot M$$



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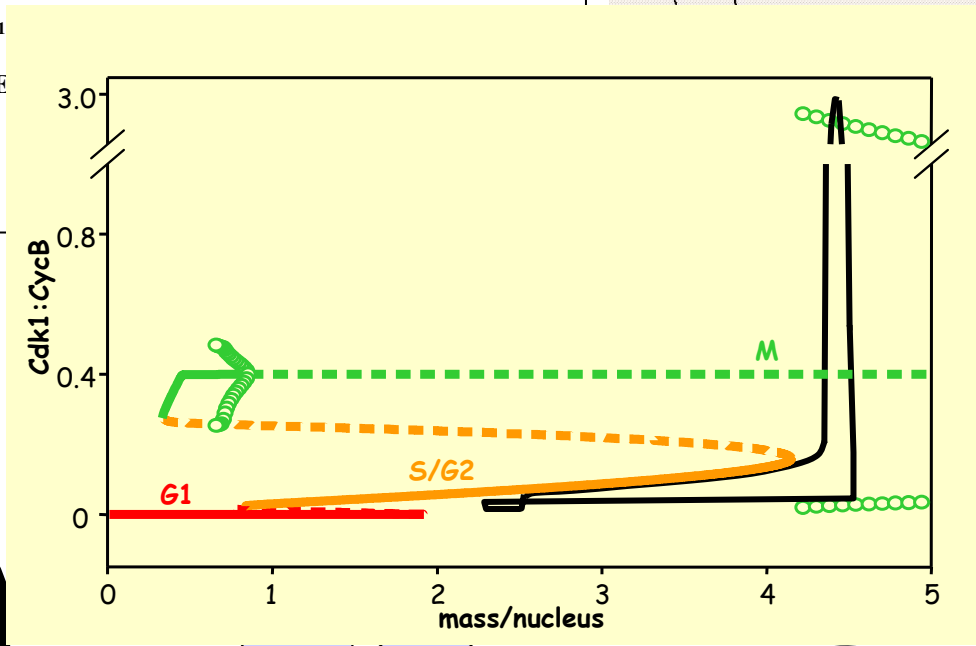
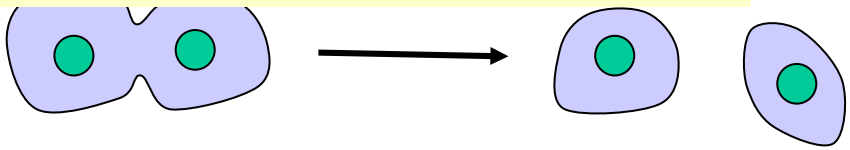




Thanks to

James S. McDonnell Found.

DARPA

References

- Tyson, Chen & Novak, “Network dynamics and cell physiology,” *Nature Rev. Molec. Cell Biol*. **2**:908 (2001).
- Tyson, Csikasz-Nagy & Novak, “The dynamics of cell cycle regulation,” *BioEssays* **24**:1095 (2002).
- Tyson, Chen & Novak, “Sniffers, buzzers, toggles and blinkers,” *Curr. Opin. Cell Biol.* **15**:221 (2003).

Computational Molecular Biology

DNA …TACCCGATGGCGAAATGC...

↓

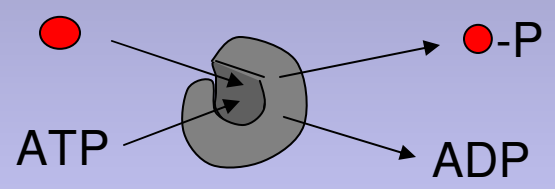
mRNA …AUGGGCUACCGCUUUACG...

↓

Protein …Met -Gly -Tyr -Arg -Phe -Thr...

↓

Enzyme



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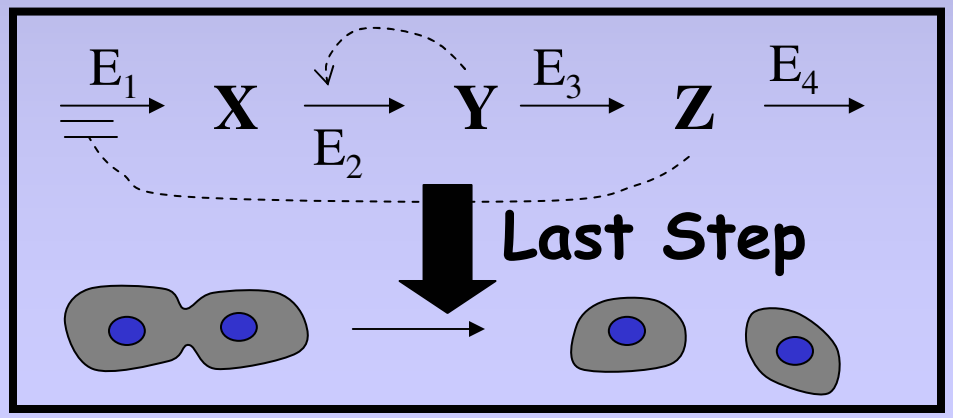
Reaction Network



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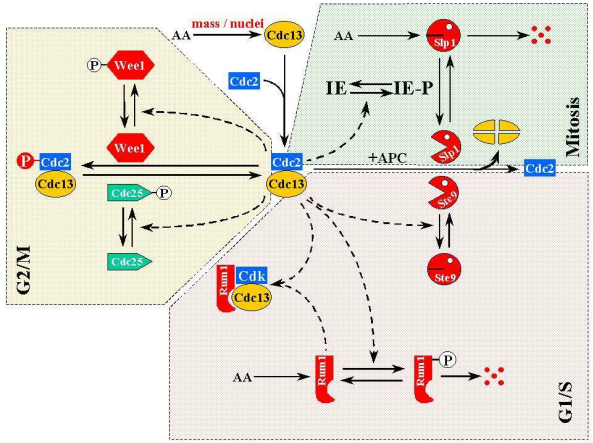
Cell Physiology

The Dynamical Perspective

Molecular Mechanism



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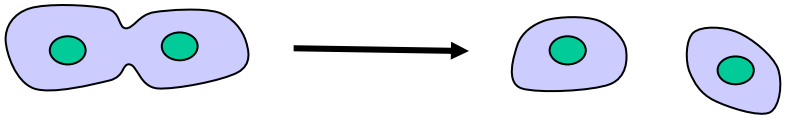
Physiological Properties



The Dynamical Perspective

Molecular Mechanism

↓

Kinetic Equations

↓

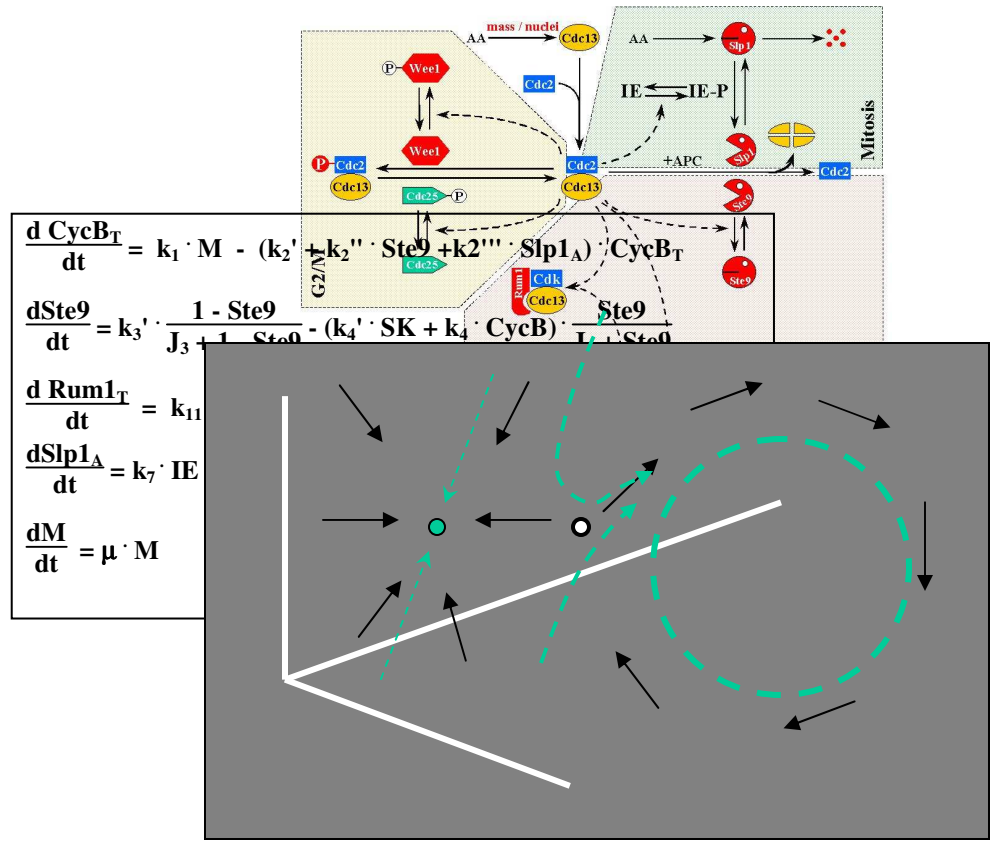
Vector Field

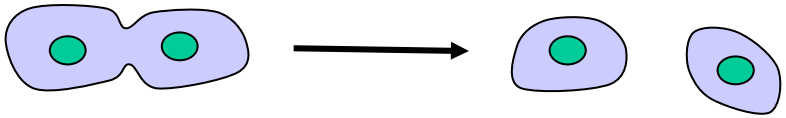
↓

Stable Attractors

↓

Physiological Properties





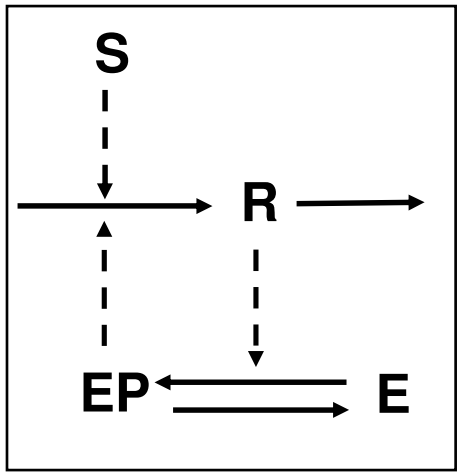
“Machine-readable” form…

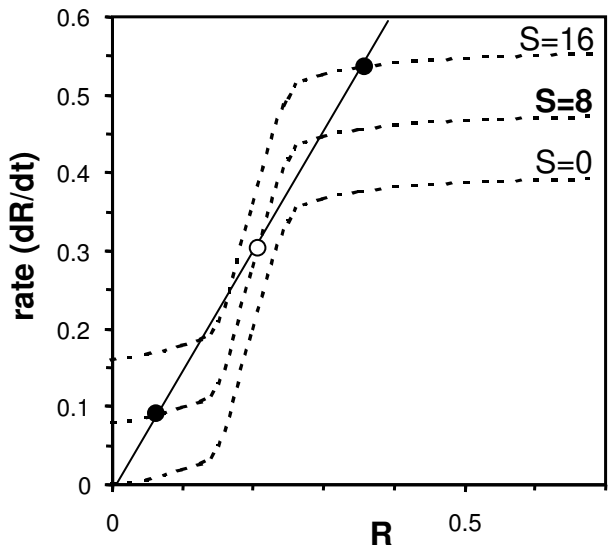
$$\frac{\mathrm{d}[\mathrm{CycA}]}{\mathrm{d}t} = \underbrace{k_1 + k_1^{'}[\mathrm{E2F}]}_{\text{synthesis}} - \underbrace{k_2[\mathrm{CycA}]}_{\text{degradation}} - \underbrace{k_5[\mathrm{CKI}][\mathrm{CycA}]}_{\text{binding}}$$

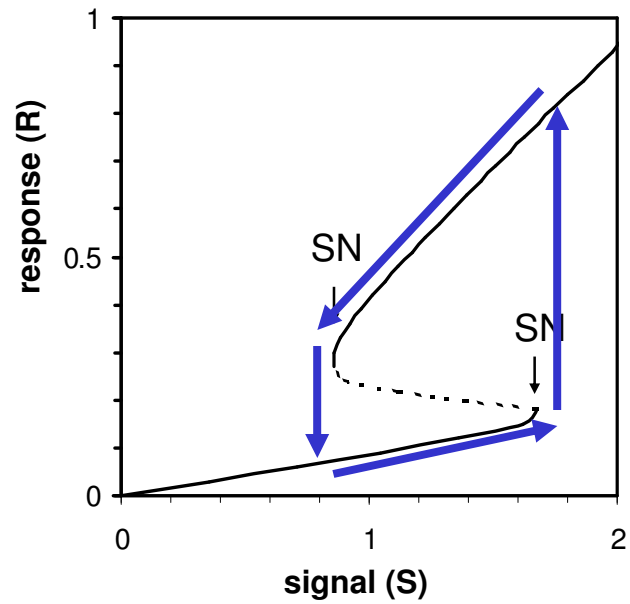
$$\frac{\mathrm{d}[\mathrm{CycB}]}{\mathrm{d}t} = \underbrace{k_3 + k_3^{'}[\mathrm{TFB}]}_{\text{synthesis}} - \underbrace{\left(k_4 + k_4^{'}[\mathrm{Cdh1}]\right)[\mathrm{CycB}]}_{\text{degradation}} - \underbrace{k_5[\mathrm{CKI}][\mathrm{CycB}]}_{\text{binding}}$$

$$\frac{\mathrm{d}[\mathrm{Cdh1}]}{\mathrm{d}t} = \underbrace{\frac{\left(k_6 + k_6^{'}[\mathrm{Cdc20}]\right)\left([\mathrm{Cdh1}]_{\mathrm{T}} - [\mathrm{Cdh1}]\right)}{J_6 + [\mathrm{Cdh1}]_{\mathrm{T}} - [\mathrm{Cdh1}]}}_{\text{activation}} - \underbrace{\frac{\left(k_7 + k_7^{'}[\mathrm{Clb5}]\right)[\mathrm{Cdh1}]}{J_7 + [\mathrm{Cdh1}]}}_{\text{inactivation}}$$

Change parameters…







"Toggle"

Griffith, 1968