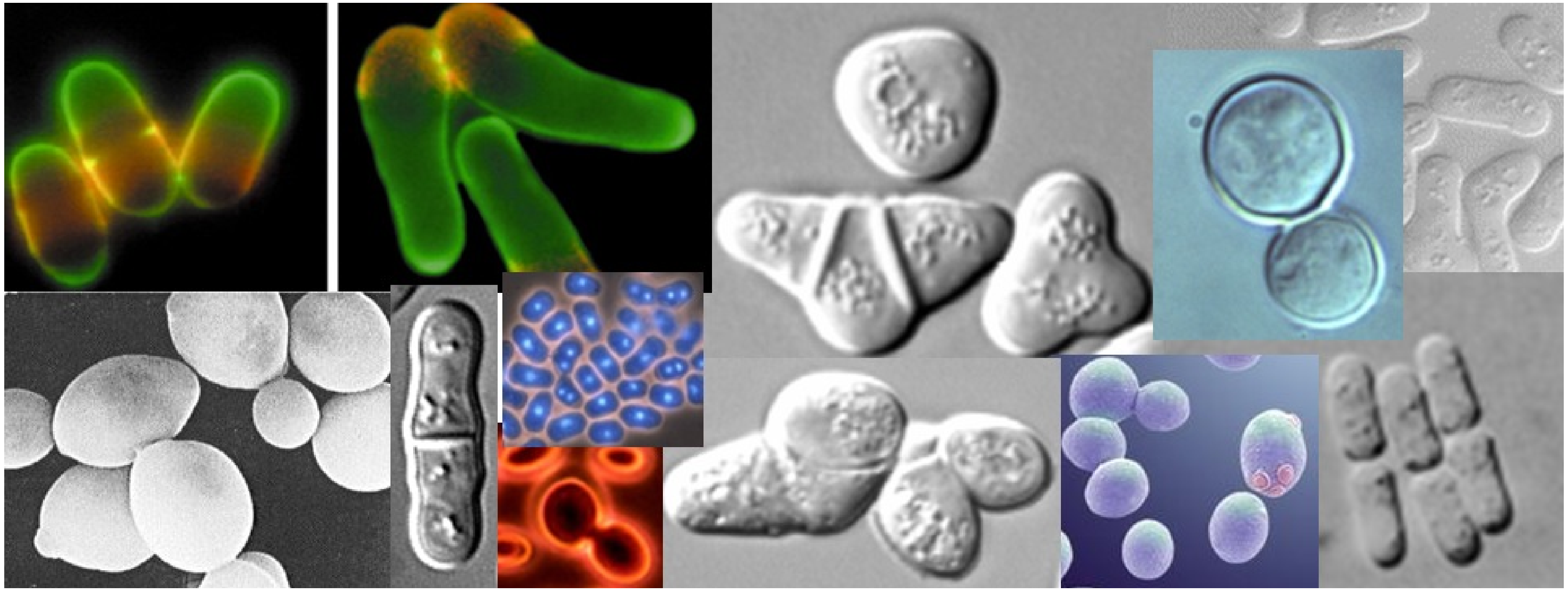
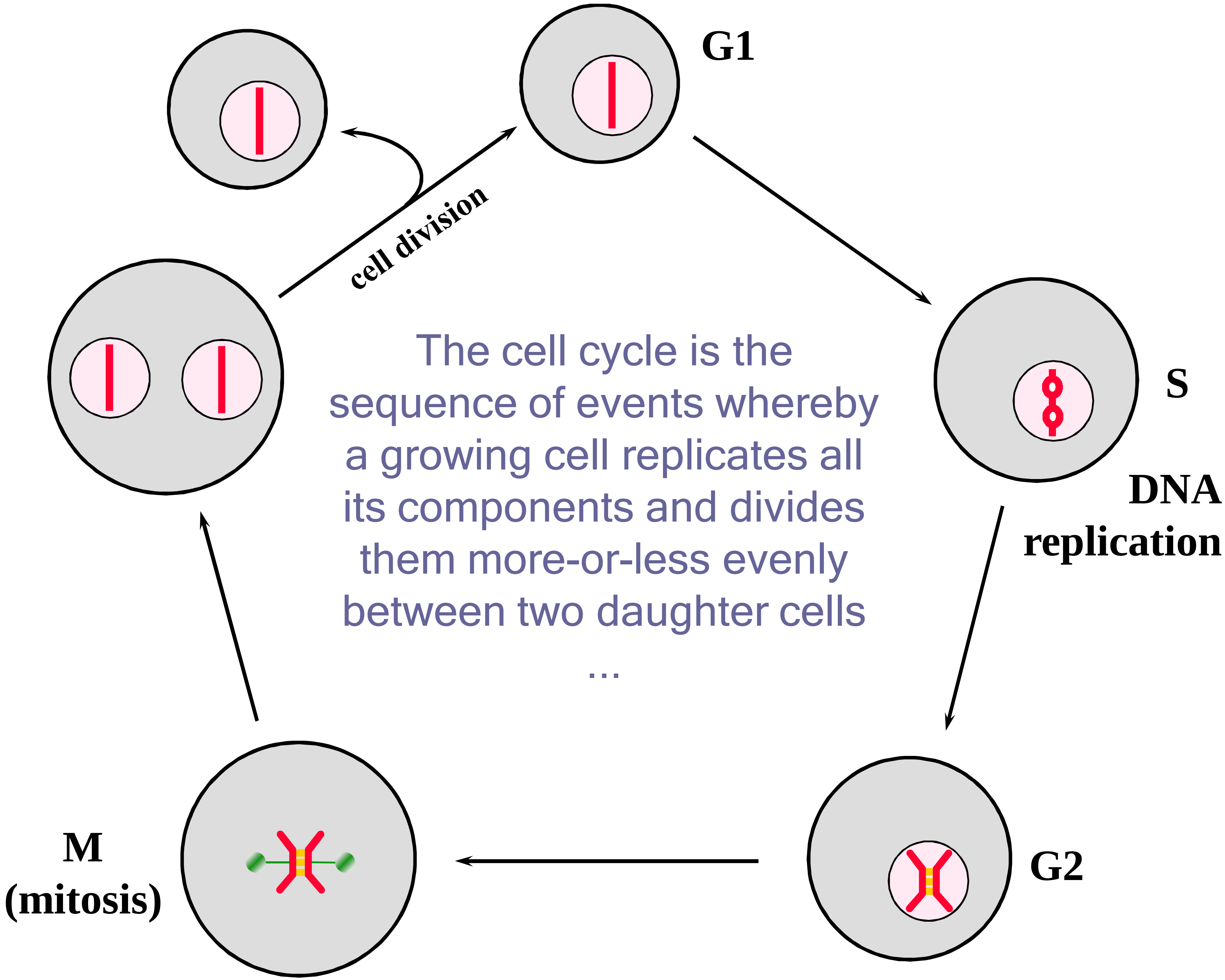
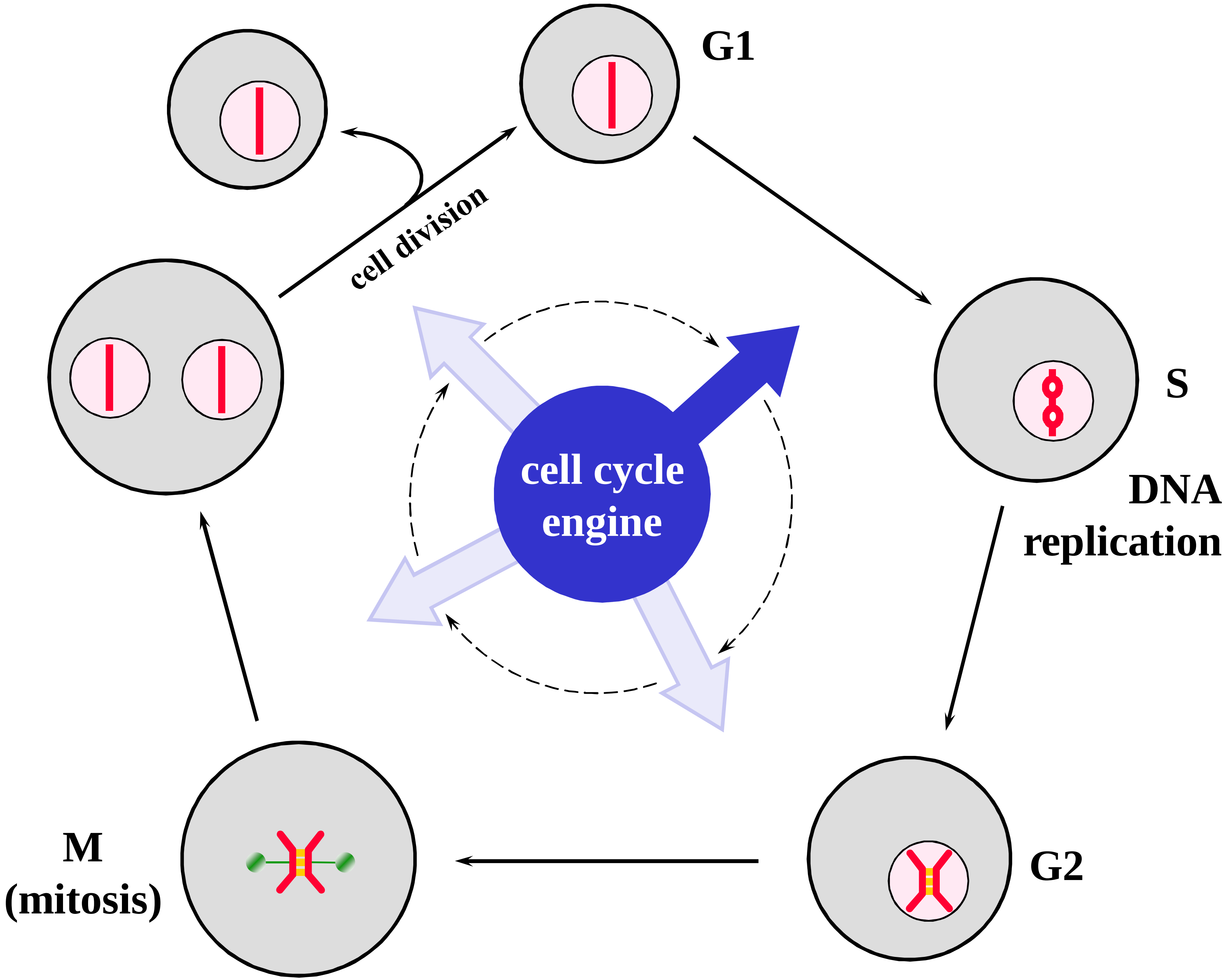
Introduction to cell cycle modeling



Attila Csikász-Nagy

The Microsoft Research - University of Trento
Centre for Computational and Systems Biology


G1
S
DNA
replication
G2
M
(mitosis)
cell division
The cell cycle is the
sequence of events whereby
a growing cell replicates all
its components and divides
them more-or-less evenly
between two daughter cells
...


G1
S
DNA
replication
G2
M
(mitosis)
cell division
cell cycle
engine

The Nobel Prize in Physiology or Medicine 2001

"for their discoveries of key regulators of the cell cycle"

Leland H. Hartwell

USA

Fred Hutchinson Cancer Research Center
Seattle, WA, USA

1939 -

R. Timothy (Tim) Hunt

Great Britain

Imperial Cancer Research Fund
London, Great Britain

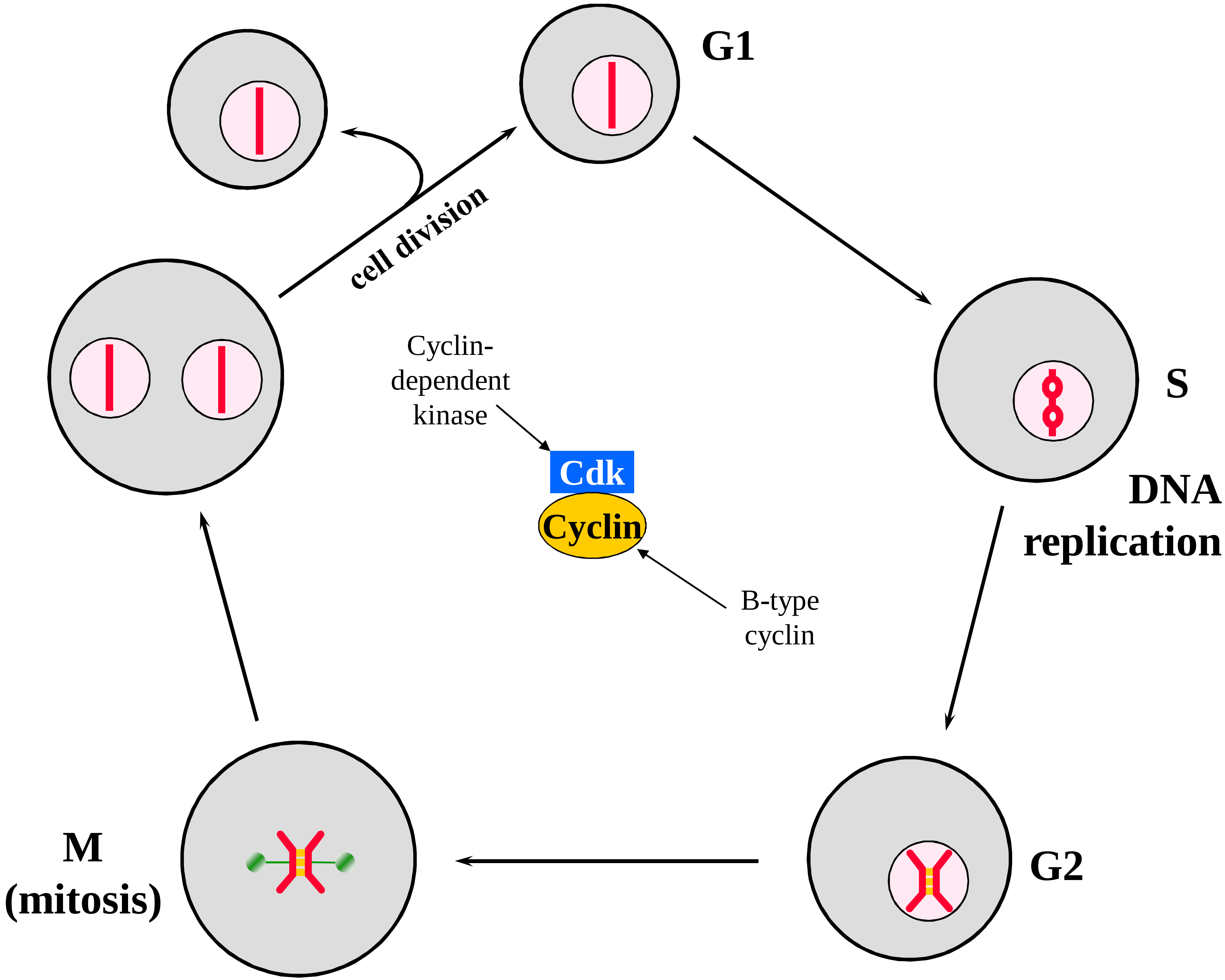
1943 -

Paul M. Nurse

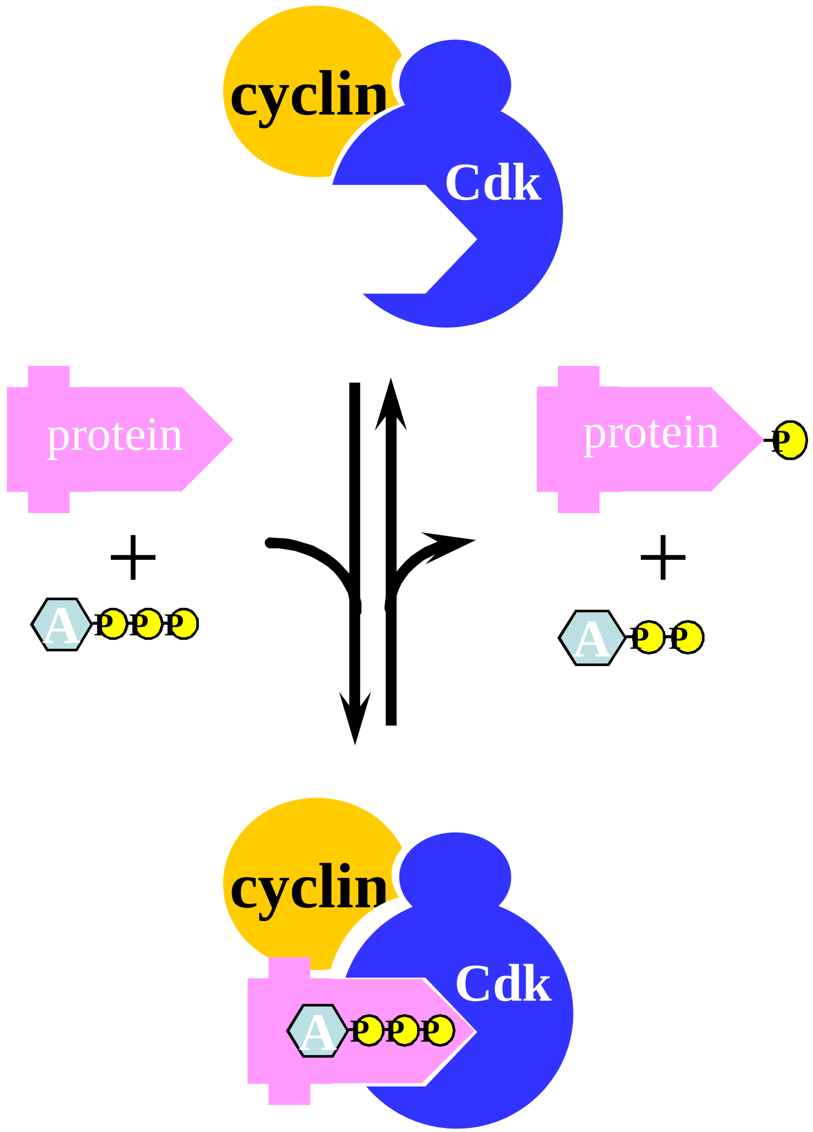
Great Britain

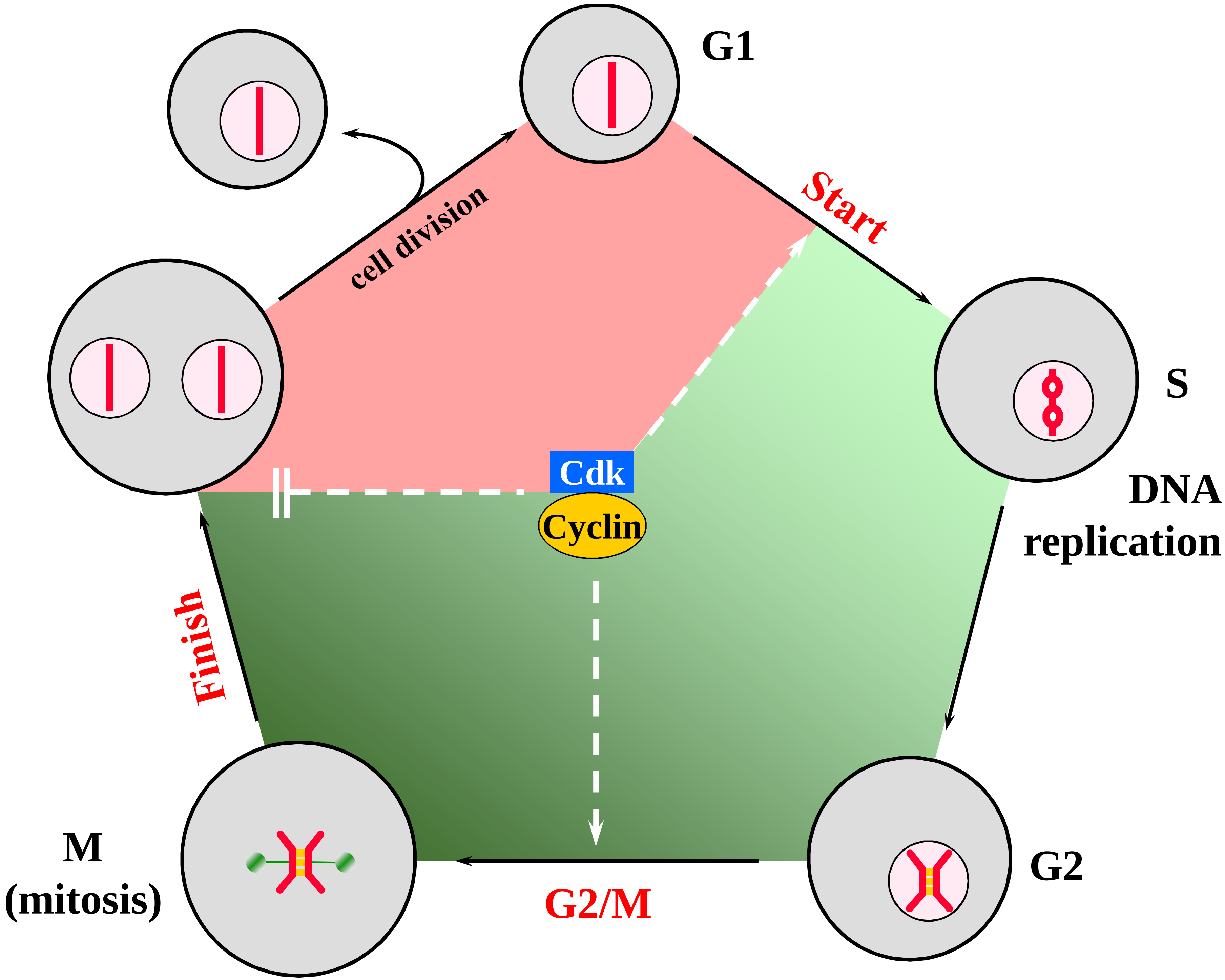
Imperial Cancer Research Fund
London, Great Britain

1949 -

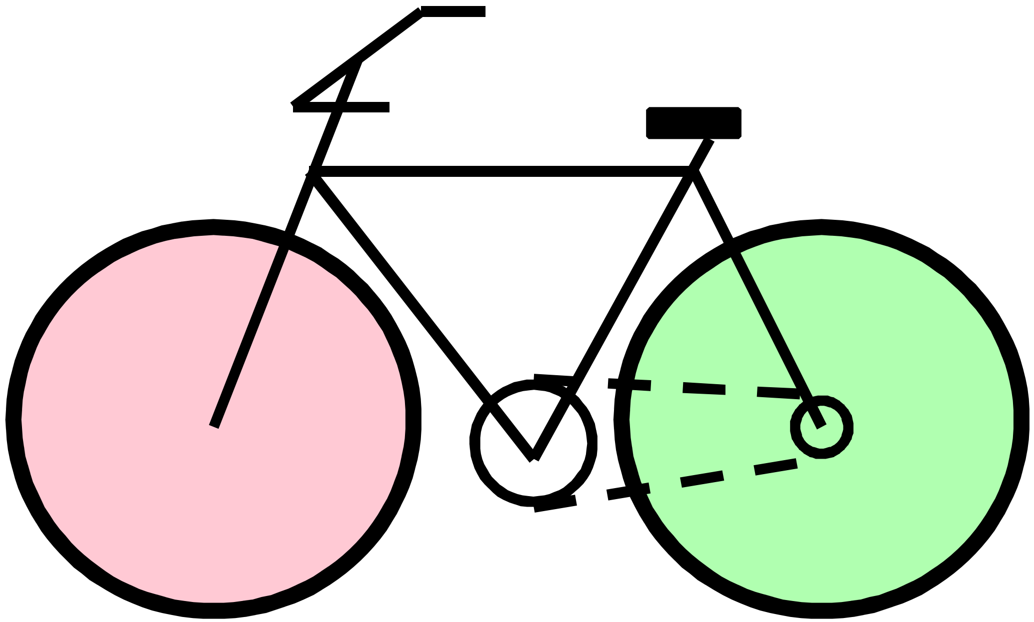

G1
cell division
Cyclin-
dependent
kinase
Cdk
Cyclin
S
DNA
replication
B-type
cyclin
M
(mitosis)
G2

Cyclin dependent protein kinase





G1
Start
S
DNA replication
G2
G2/M
M (mitosis)
Finish
cell division
Cdk
Cyclin

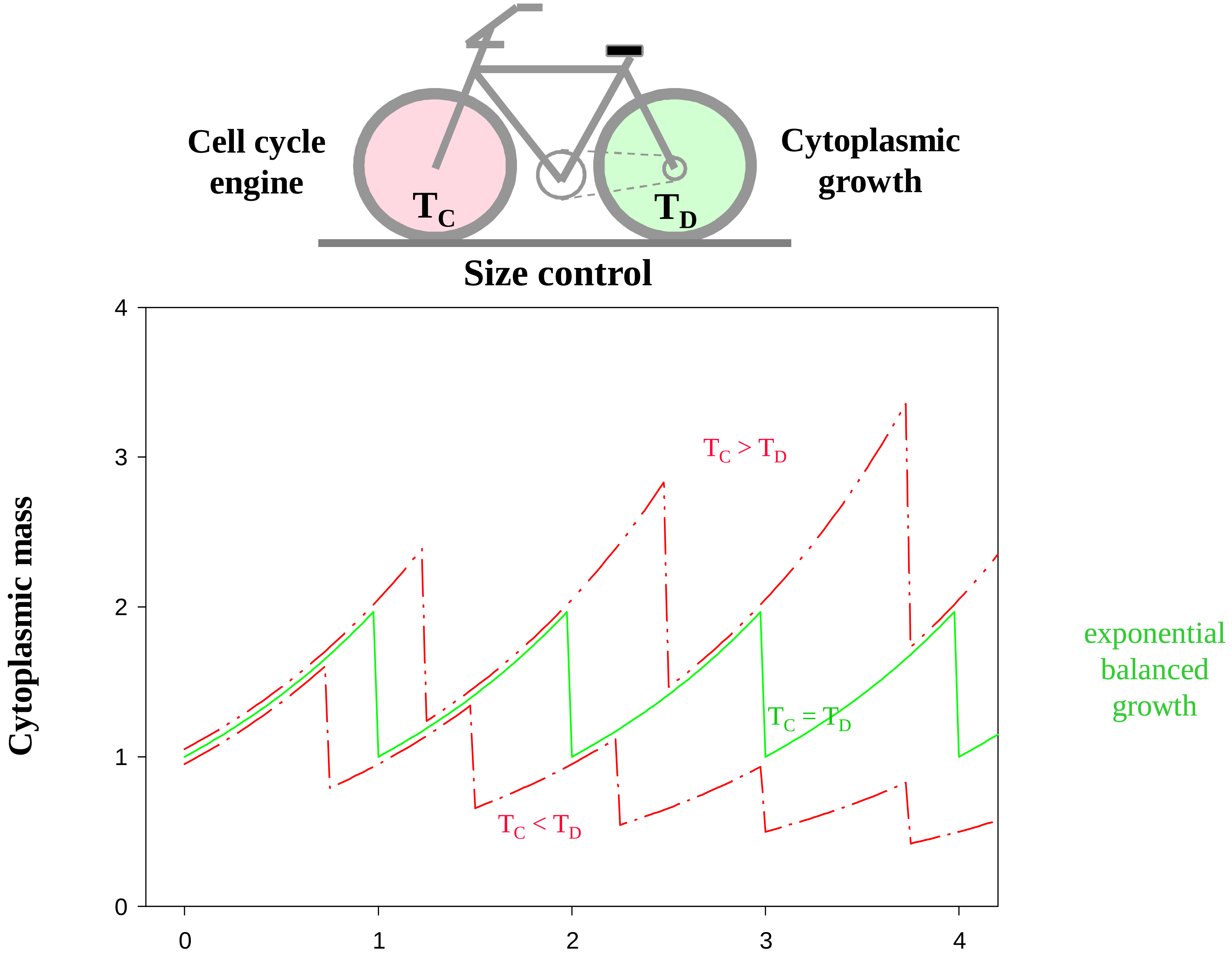


chromosome cycle

- **DNA replication**
- **mitosis**
  (precise doubling and halving)

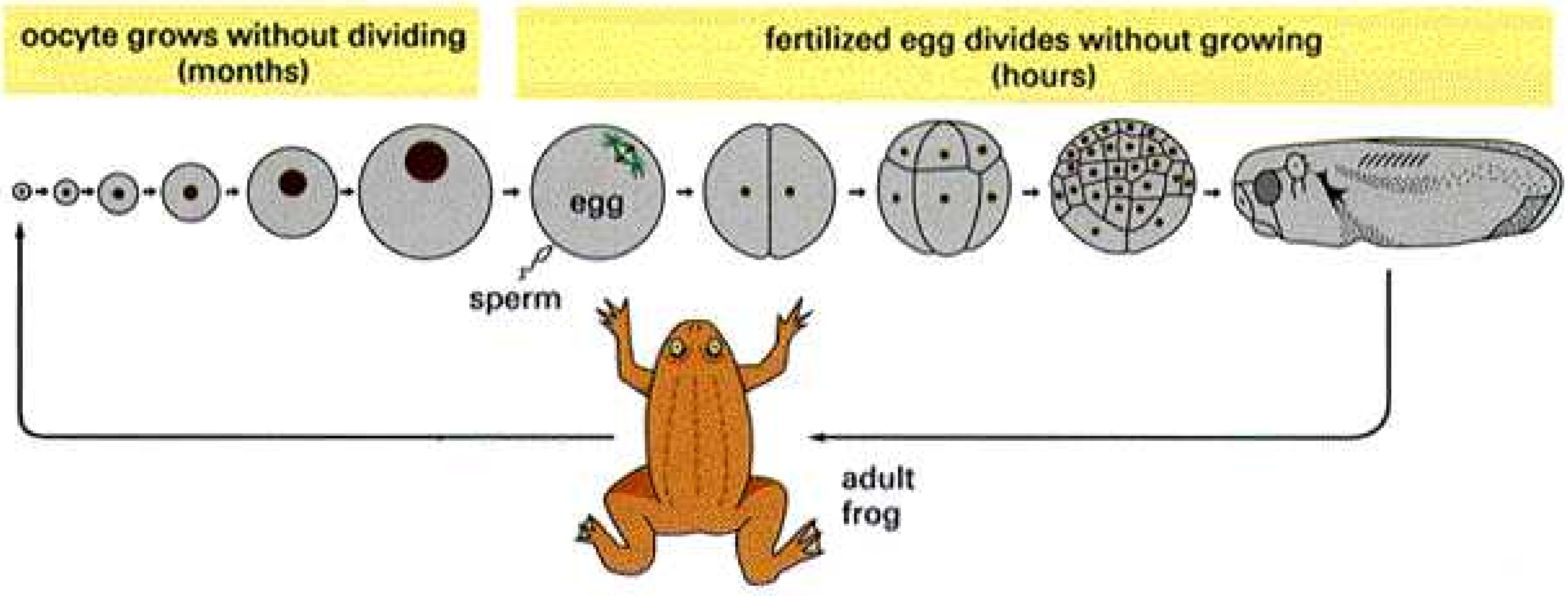
growth cycle

- **cell growth**
- **cell division**
  (approx. doubling and halving)


Cell cycle engine
Cytoplasmic growth
T_C
T_D
Size control
Cytoplasmic mass
0
1
2
3
4
T_C > T_D
T_C = T_D
T_C < T_D
exponential balanced growth

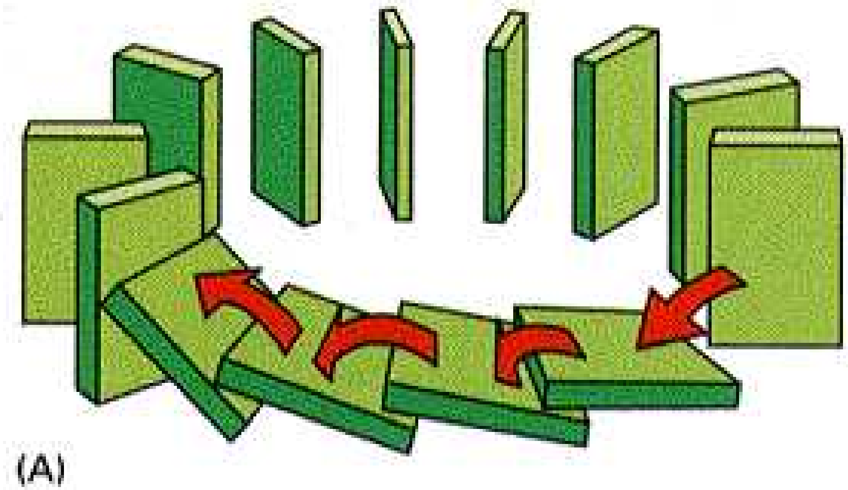
Uncoupling of the growth and chromosomal cycles

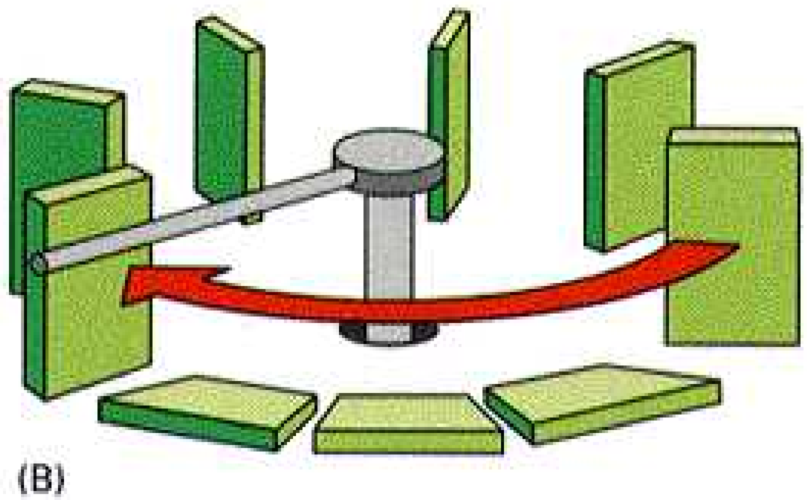
oogenesis **embryogenesis**



growing (somatic) cells

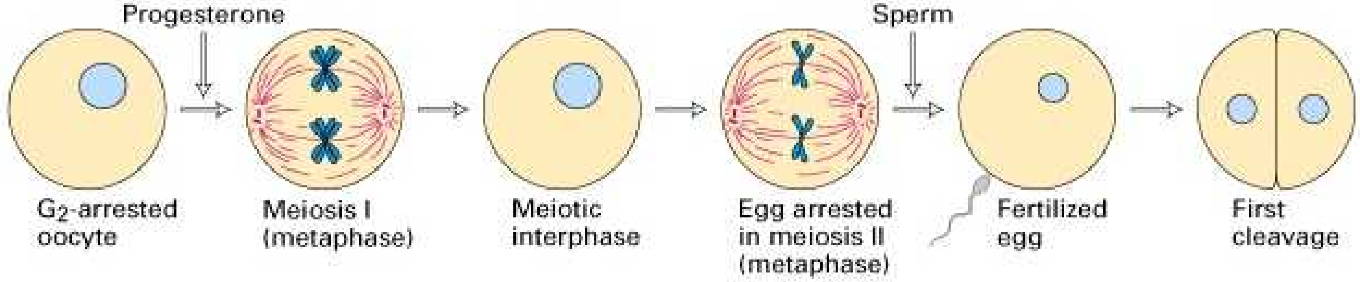
early embryos



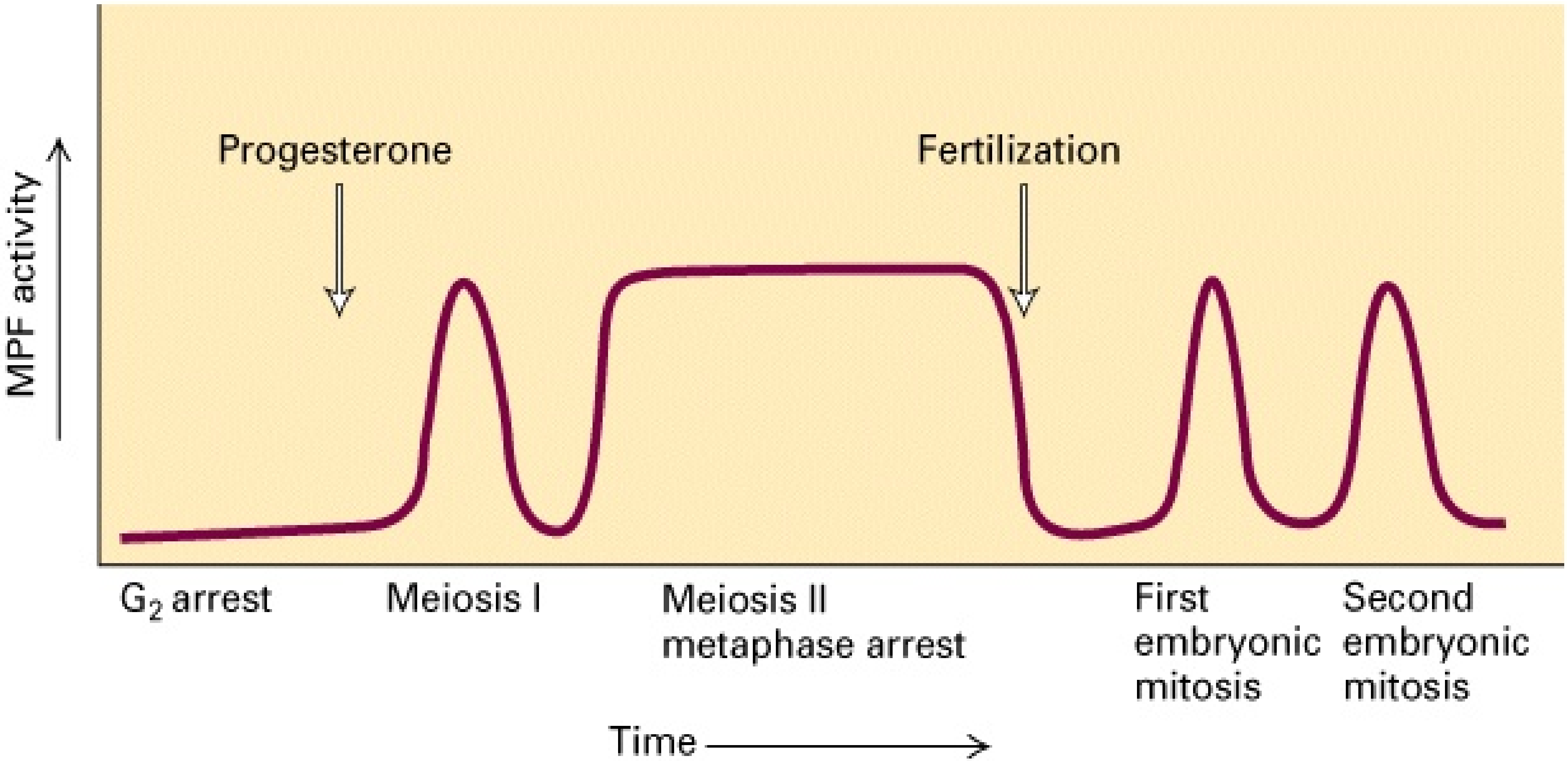


Modeling cell cycle regulation

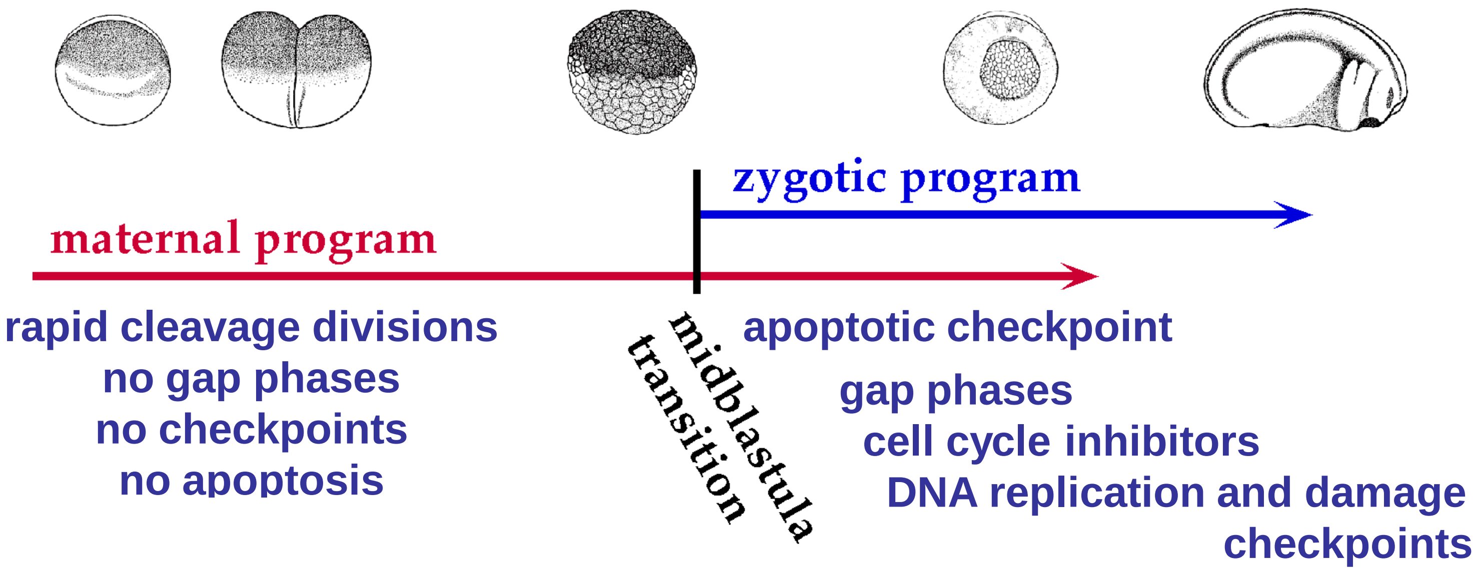
I. Embryonic cycles



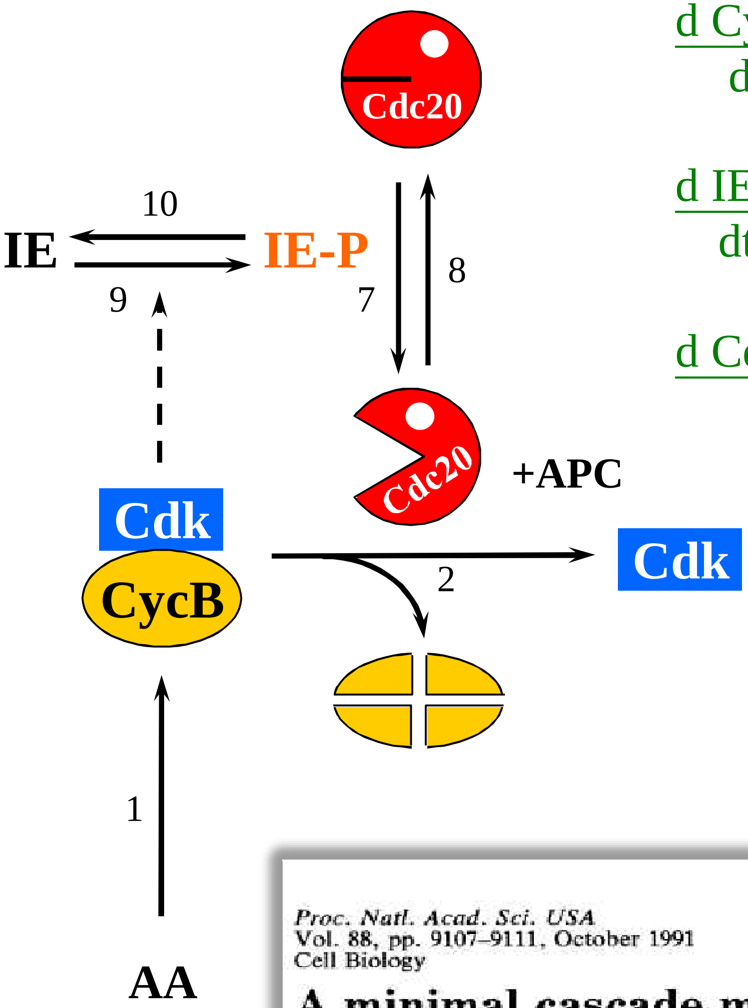
Yoshio Masui



Cell cycle remodeling begins at the MBT.



The negative feedback loop



$$\frac{d\,CycB}{dt} = k_1 - (k_2' + k_2'' \cdot Cdc20_A)\,CycB$$

$$\frac{d\,IE\text{-}P}{dt} = k_9 \cdot CycB \cdot \frac{1 - IE\text{-}P}{J_9 + 1 - IE\text{-}P} - k_{10} \cdot \frac{IE\text{-}P}{J_{10} + IE\text{-}P}$$

$$\frac{d\,Cdc20_A}{dt} = k_7 \cdot IE\text{-}P \cdot \frac{1 - Cdc20_A}{J_7 + 1 - Cdc20_A} - k_8 \cdot \frac{Cdc20_A}{J_8 + Cdc20_A}$$

Proc. Natl. Acad. Sci. USA
Vol. 88, pp. 9107–9111, October 1991
Cell Biology

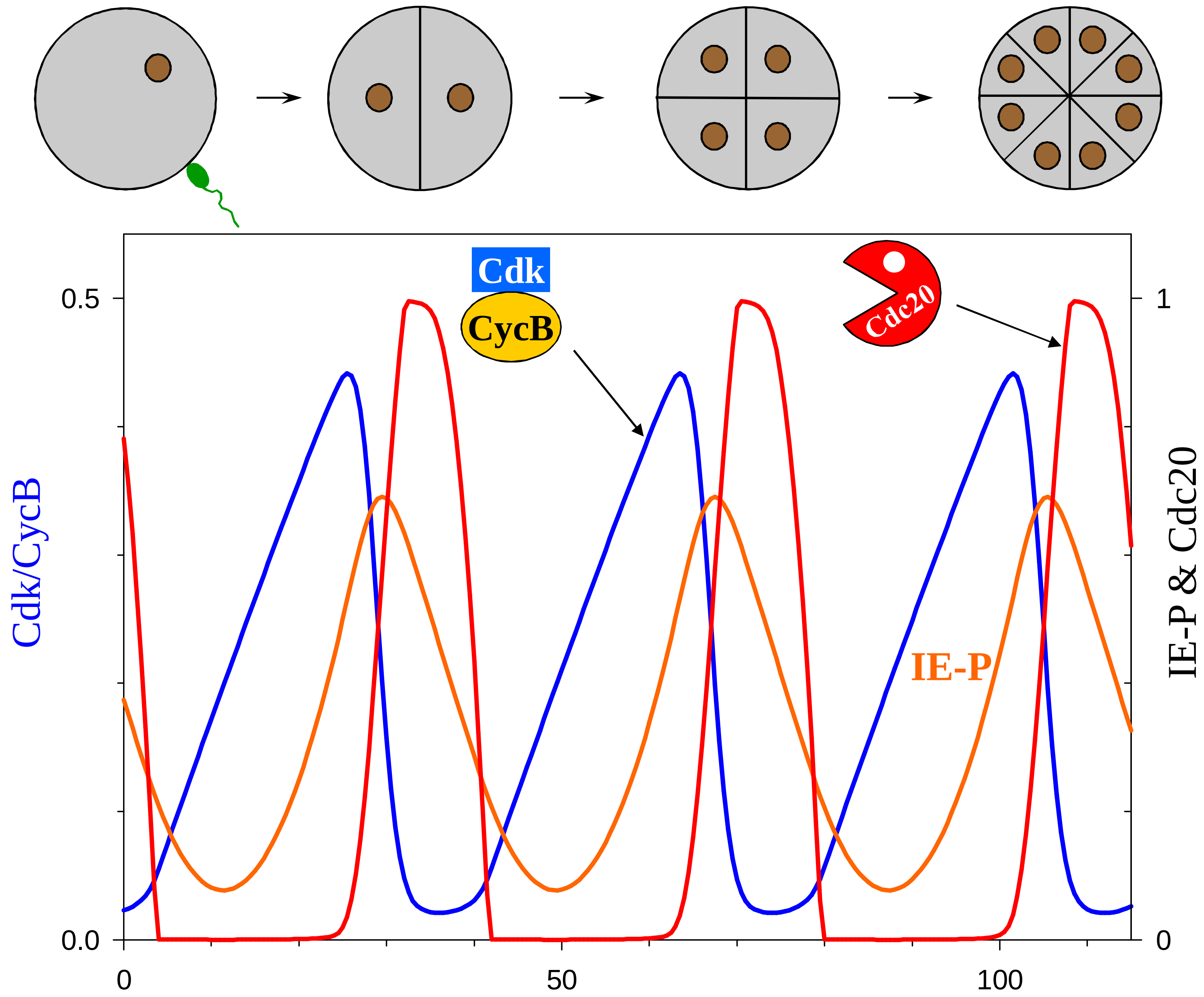
A minimal cascade model for the mitotic oscillator involving cyclin and cdc2 kinase

(cell cycle/maturation-promoting factor/phosphorylation cascade/thresholds/biochemical oscillations)

ALBERT GOLDBETER

Faculté des Sciences, Université Libre de Bruxelles, Campus Plaine, C.P. 231, B-1050 Brussels, Belgium

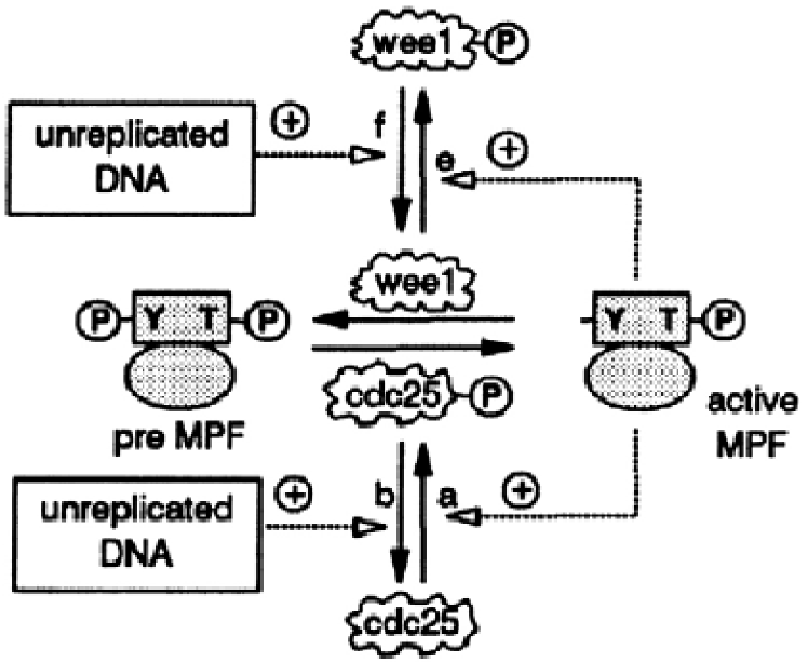
Early embryonic cell cycles

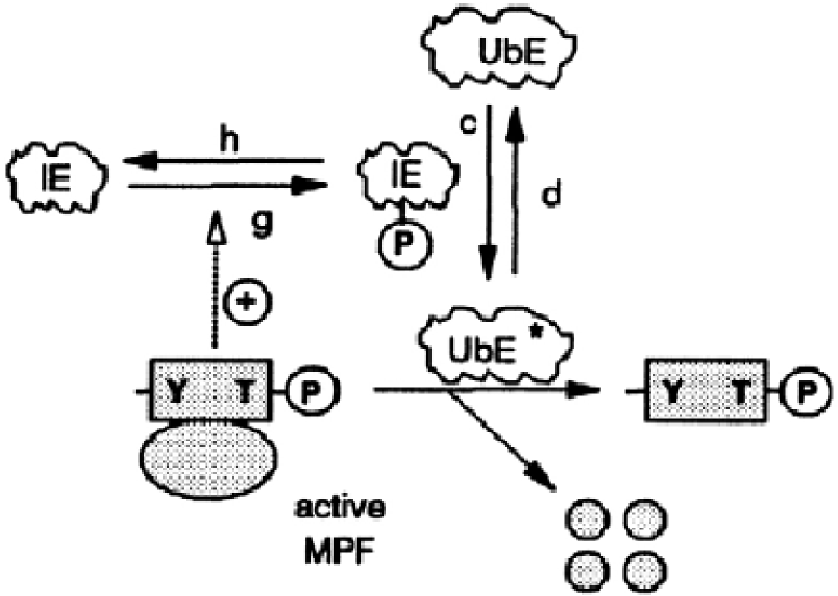


Journal of Cell Science 106, 1153-1168 (1993)

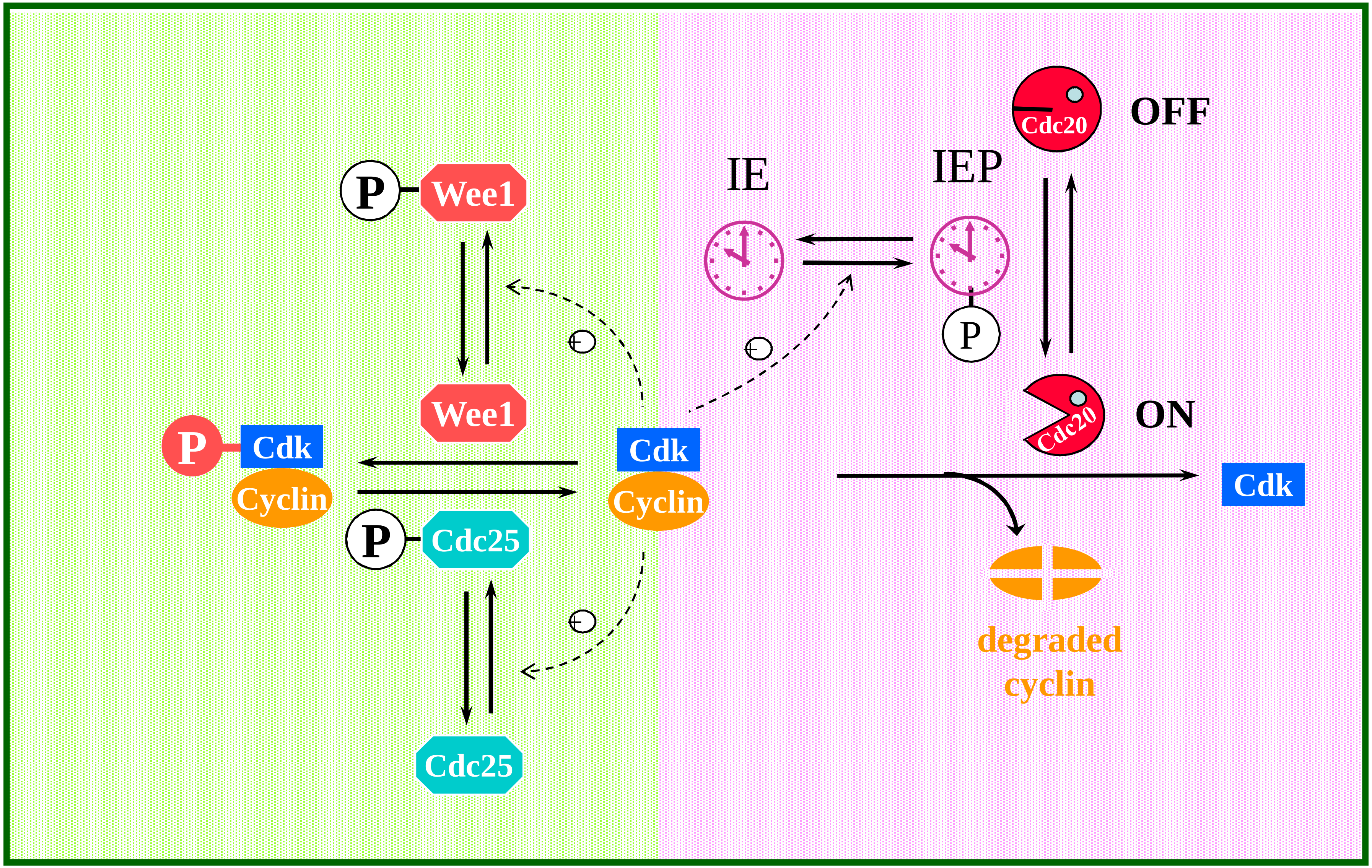
Numerical analysis of a comprehensive model of M-phase control in *Xenopus* oocyte extracts and intact embryos

Bela Novak* and John J. Tyson†





MPF is regulated by positive and negative feedback loops



Direct negative feedback:

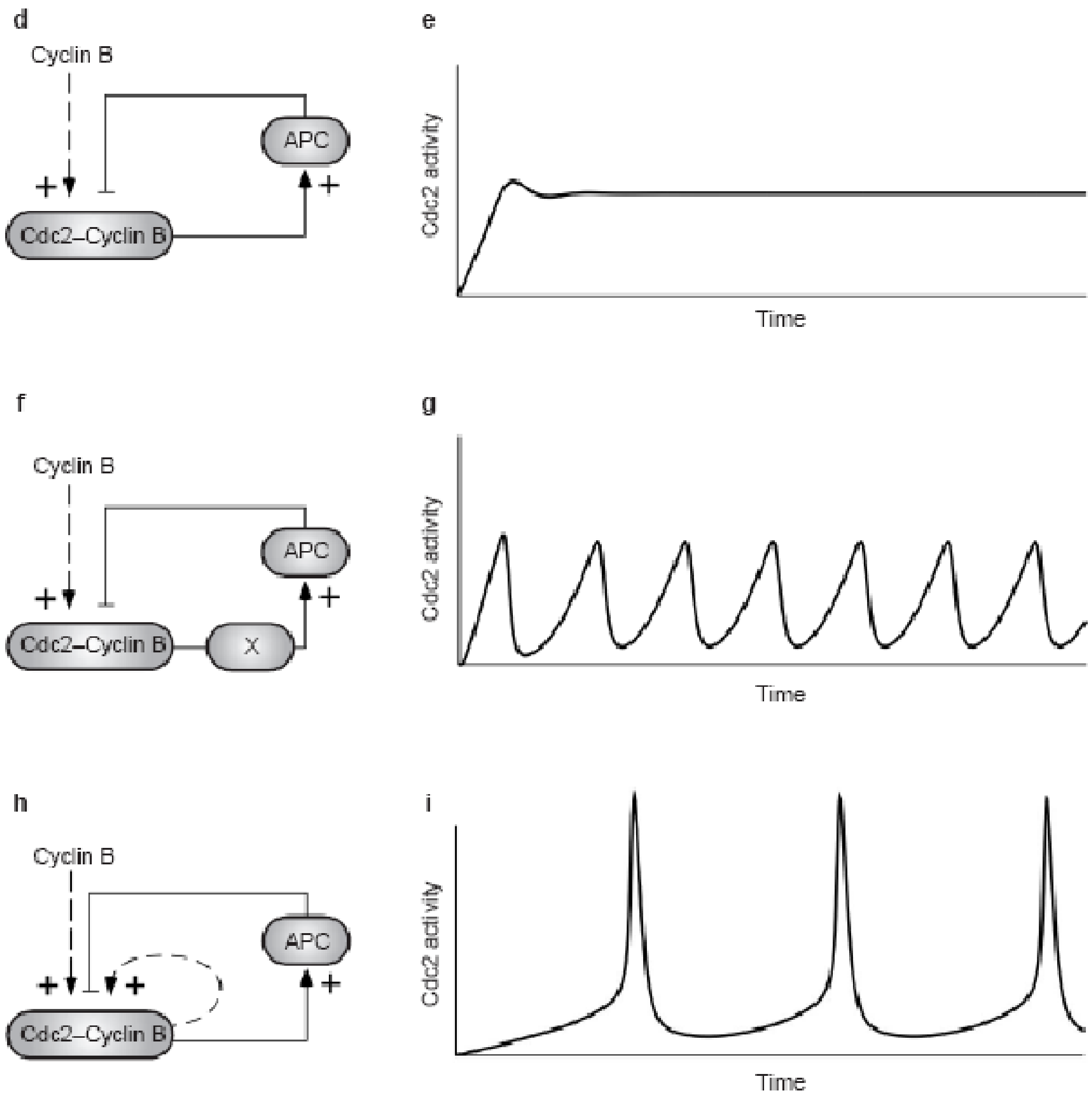
NO oscillations

Delayed negative feedback:

sinusoid oscillations

Positive & negative feedbacks:

relaxation oscillations



Differential Equations in Novak-Tyson Model

$$\frac{d[Cyclin]}{dt} = k_1 - k_2[Cyclin] - k_3[Cdk1][Cyclin]$$

$$\frac{d[YT]}{dt} = k_{pp}[MPF] - (k_{wee} + k_{cak} + k_2)[YT] + k_{25}[PYT] + k_3[Cdk1][Cyclin]$$

$$\frac{d[PYT]}{dt} = k_{wee}[YT] - (k_{25} + k_{cak} + k_2)[PYT] + k_{pp}[PYTP]$$

$$\frac{d[PYTP]}{dt} = k_{wee}[MPF] - (k_{pp} + k_{25} + k_2)[PYTP] + k_{cak}[PYT]$$

$$\frac{d[MPF]}{dt} = k_{cak}[YT] - (k_{pp} + k_{wee} + k_2)[MPF] + k_{25}[PYTP]$$

$$\frac{d[Cdc25P]}{dt} = \frac{k_a[MPF]([total\ Cdc25] - [Cdc25P])}{K_a + [total\ Cdc25] - [Cdc25P]} - \frac{k_b[PPase][Cdc25P]}{K_b + [Cdc25P]}$$

$$\frac{d[Wee1P]}{dt} = \frac{k_e[MPF]([total\ Wee1] - [Wee1P])}{K_e + [total\ Wee1] - [Wee1P]} - \frac{k_f[PPase][Wee1P]}{K_f + [Wee1P]}$$

$$\frac{d[IEP]}{dt} = \frac{k_g[MPF]([total\ IE] - [IEP])}{K_g + [total\ IE] - [IEP]} - \frac{k_h[PPase][IEP]}{K_h + [IEP]}$$

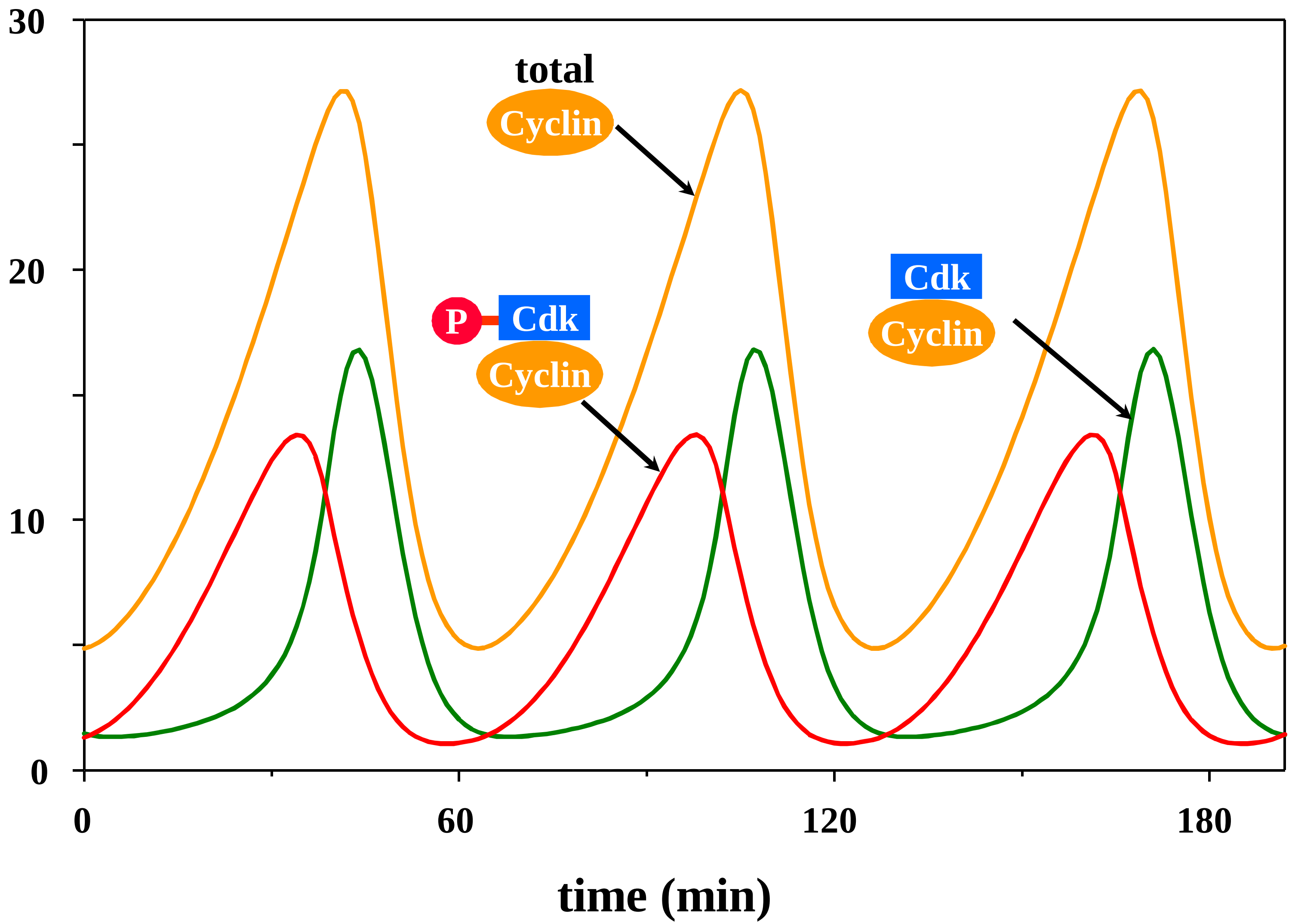
$$\frac{d[APC^*]}{dt} = \frac{k_c[IEP]([total\ APC] - [APC^*])}{K_c + [total\ APC] - [APC^*]} - \frac{k_d[Anti\ IE][APC^*]}{K_d + [APC^*]}$$

$$k_{25} = V_{25}'([total\ Cdc25] - [Cdc25P]) + V_{25}''[Cdc25P]$$

$$k_{wee} = V_{wee}'[Wee1P] + V_{wee}''([total\ Wee1] - [Wee1P])$$

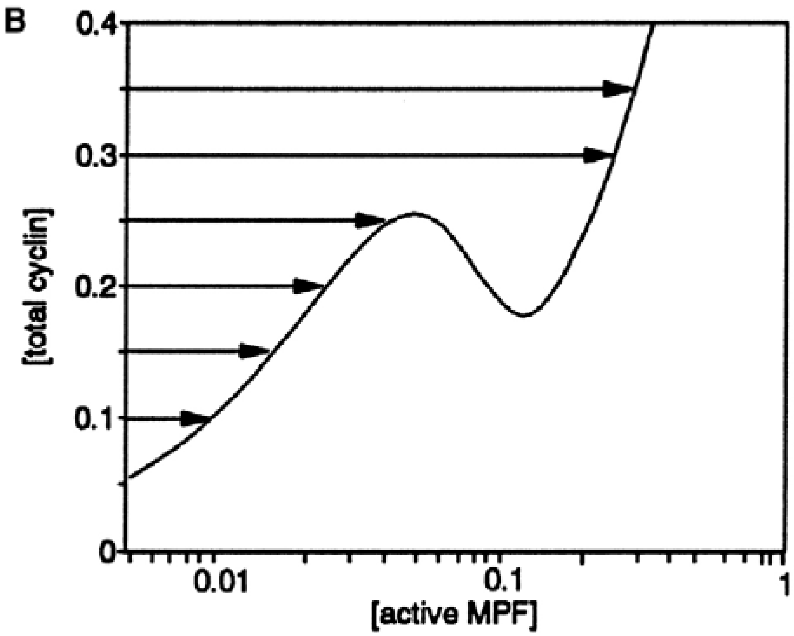
$$k_2 = V_2'([total\ APC] - [APC^*]) + V_2''[APC^*]$$

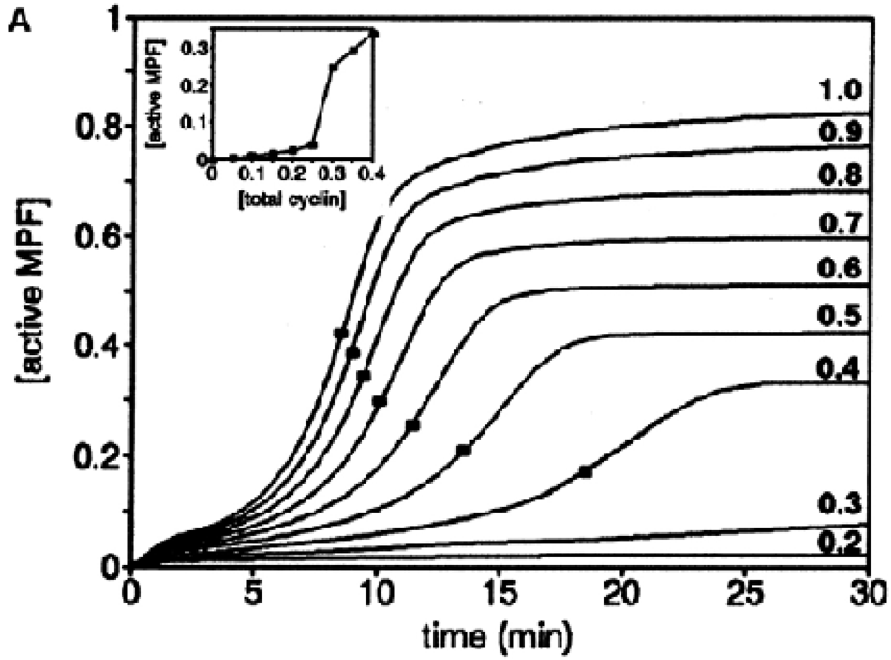
Mathematical simulations generate oscillations in the model of *Xenopus* extracts



Cyclin threshold to induce mitosis

Marc Solomon

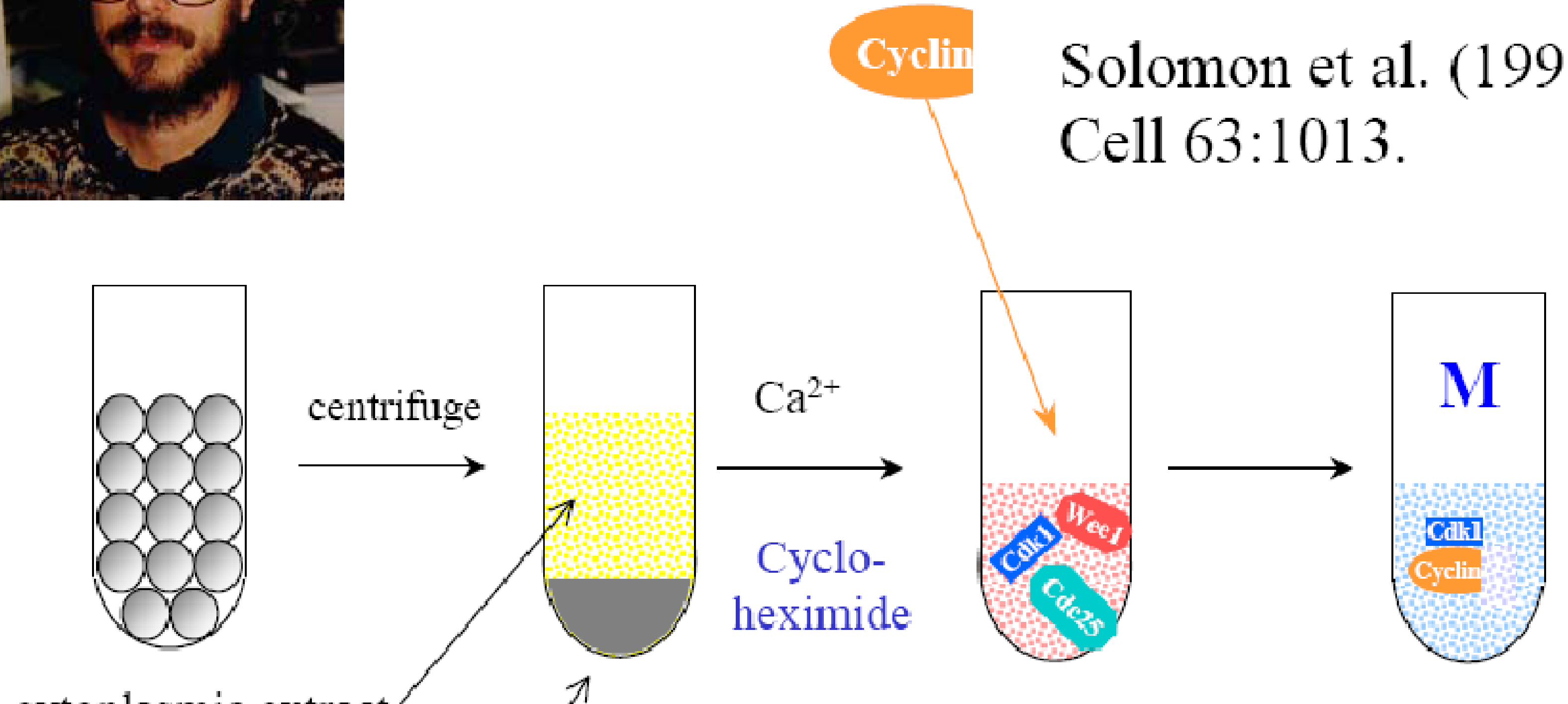


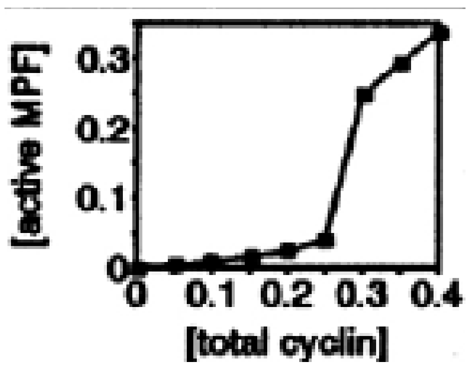


Solomon, M. J., Glotzer, M., Lee, T. H., Phillippe, M. & Kirschner, M. W. (1990) *Cell* 63, 1013–1024.

Solomon's protocol for cyclin-induced activation of CDK

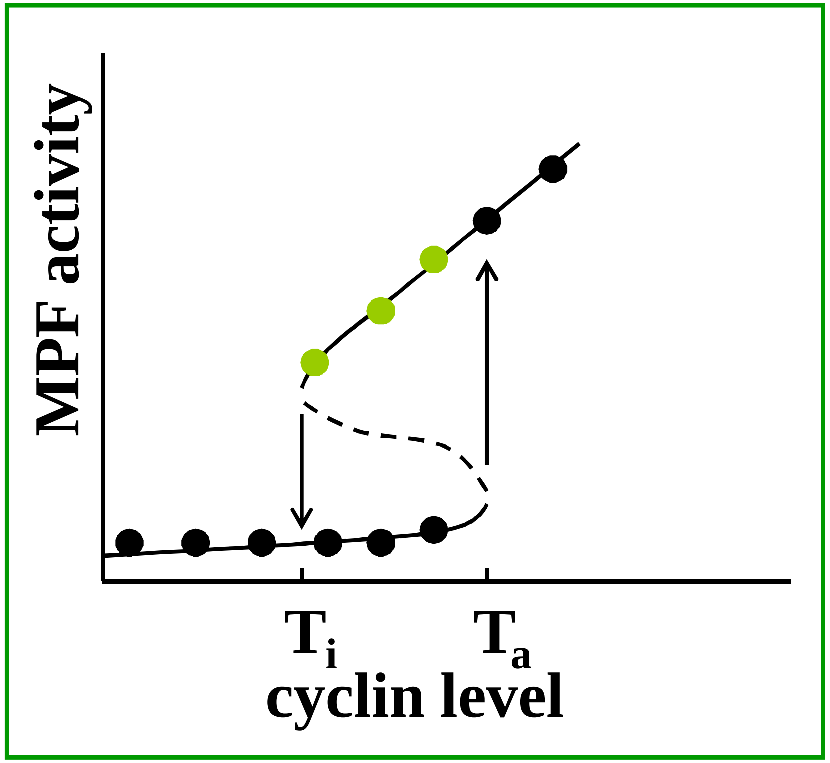
Solomon et al. (1990) Cell 63:1013.



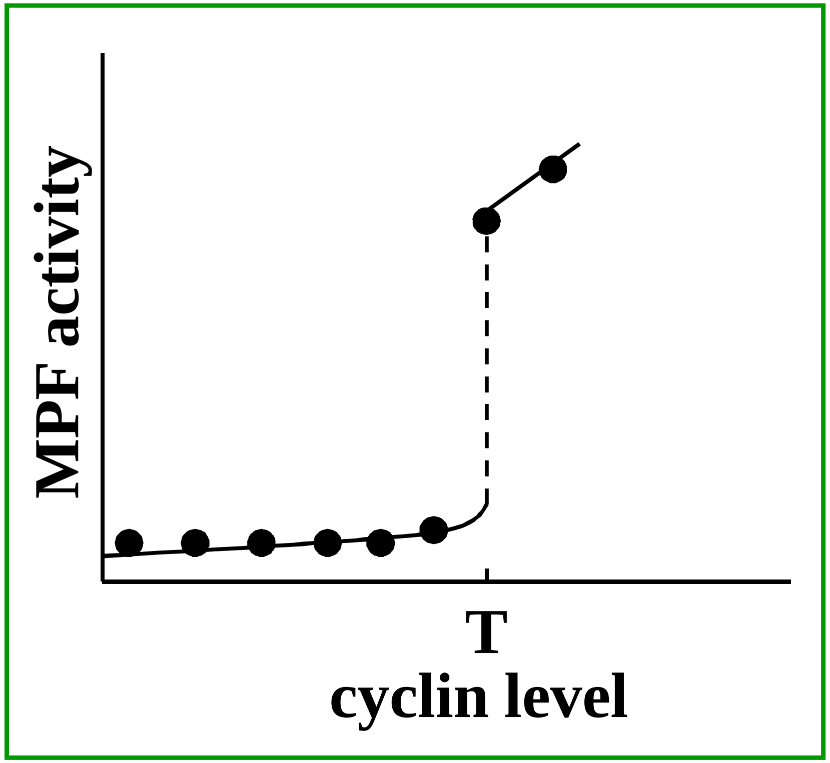


Prediction: The threshold concentration of cyclin B required to activate MPF is higher than the threshold concentration required to inactivate MPF.

hysteretic



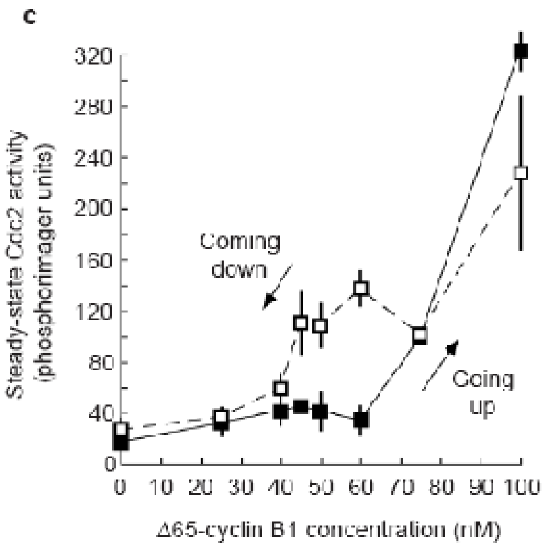
non-hysteretic



NATURE CELL BIOLOGY

Building a cell cycle oscillator: hysteresis and bistability in the activation of Cdc2

Joseph R. Pomerening*, Eduardo D. Sontag† and James E. Ferrell Jr*‡



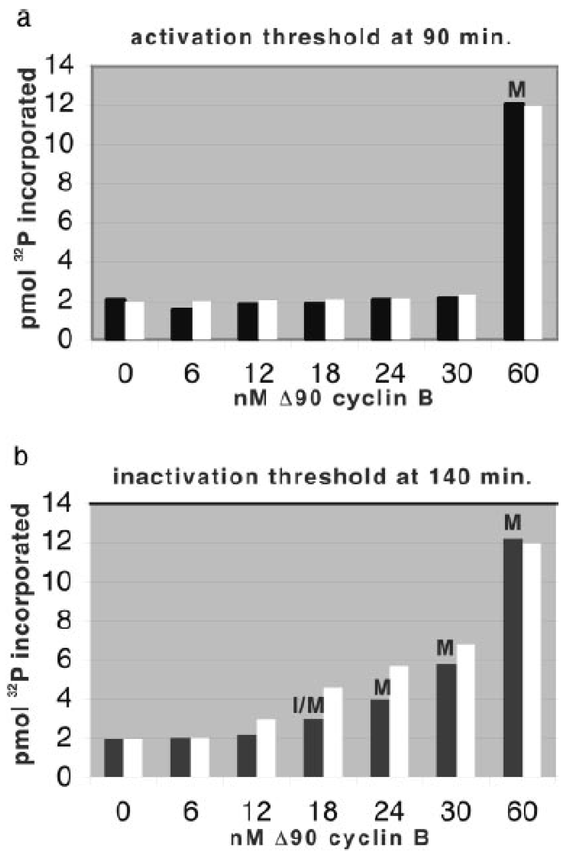
Joe Pomerening

PNAS | February 4, 2003 | vol. 100 | no. 3 | 975–980

Hysteresis drives cell-cycle transitions in *Xenopus laevis* egg extracts

Wei Sha*, Jonathan Moore†, Katherine Chen*, Antonio D. Lassaletta*, Chung-Seon Yi*, John J. Tyson*, and Jill C. Sible*‡

Jill Sible

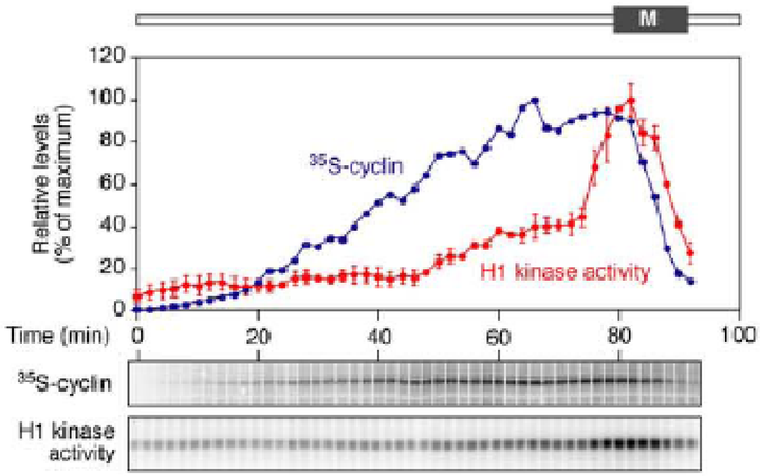


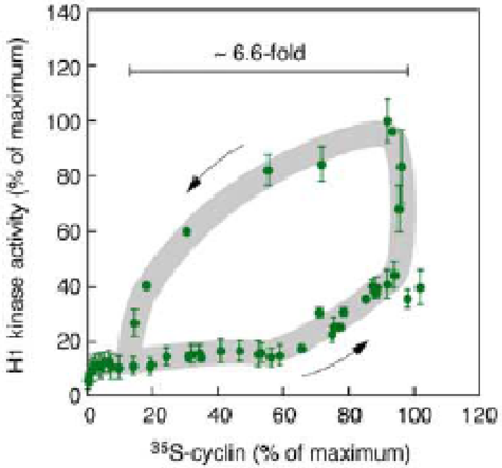
Cell, Vol. 122, 565–578, August 26, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.cell.2005.06.016

Systems-Level Dissection of the Cell-Cycle Oscillator: Bypassing Positive Feedback Produces Damped Oscillations

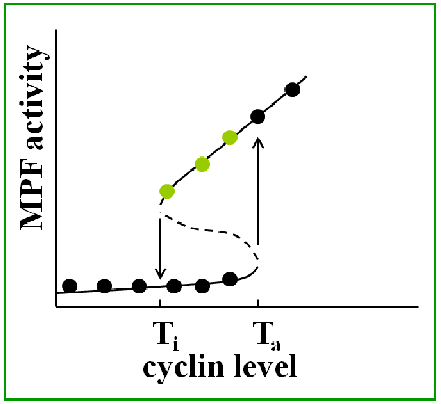
Joseph R. Pomerening,* Sun Young Kim,
and James E. Ferrell, Jr.

Joe Pomerening

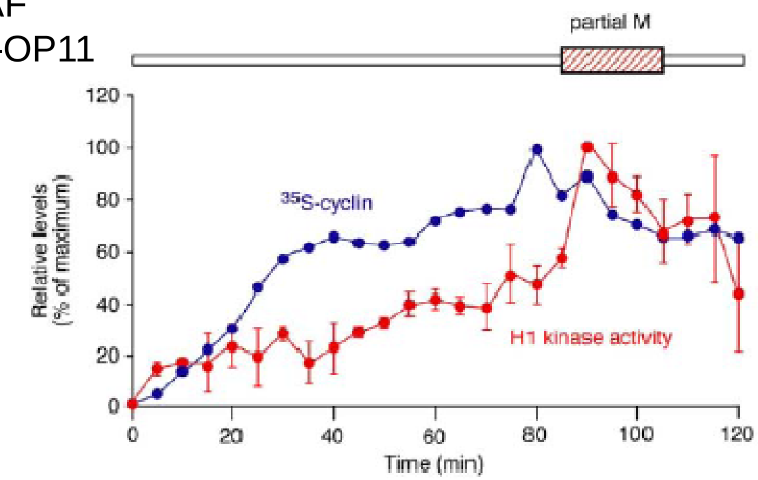


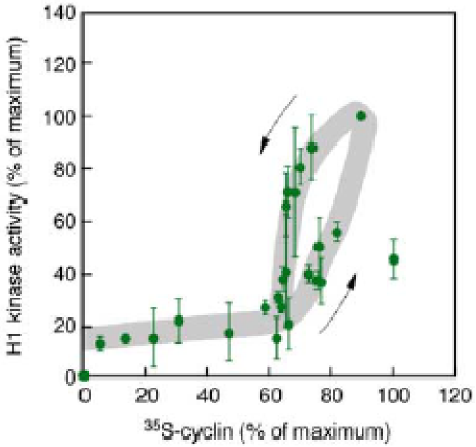


hysteretic



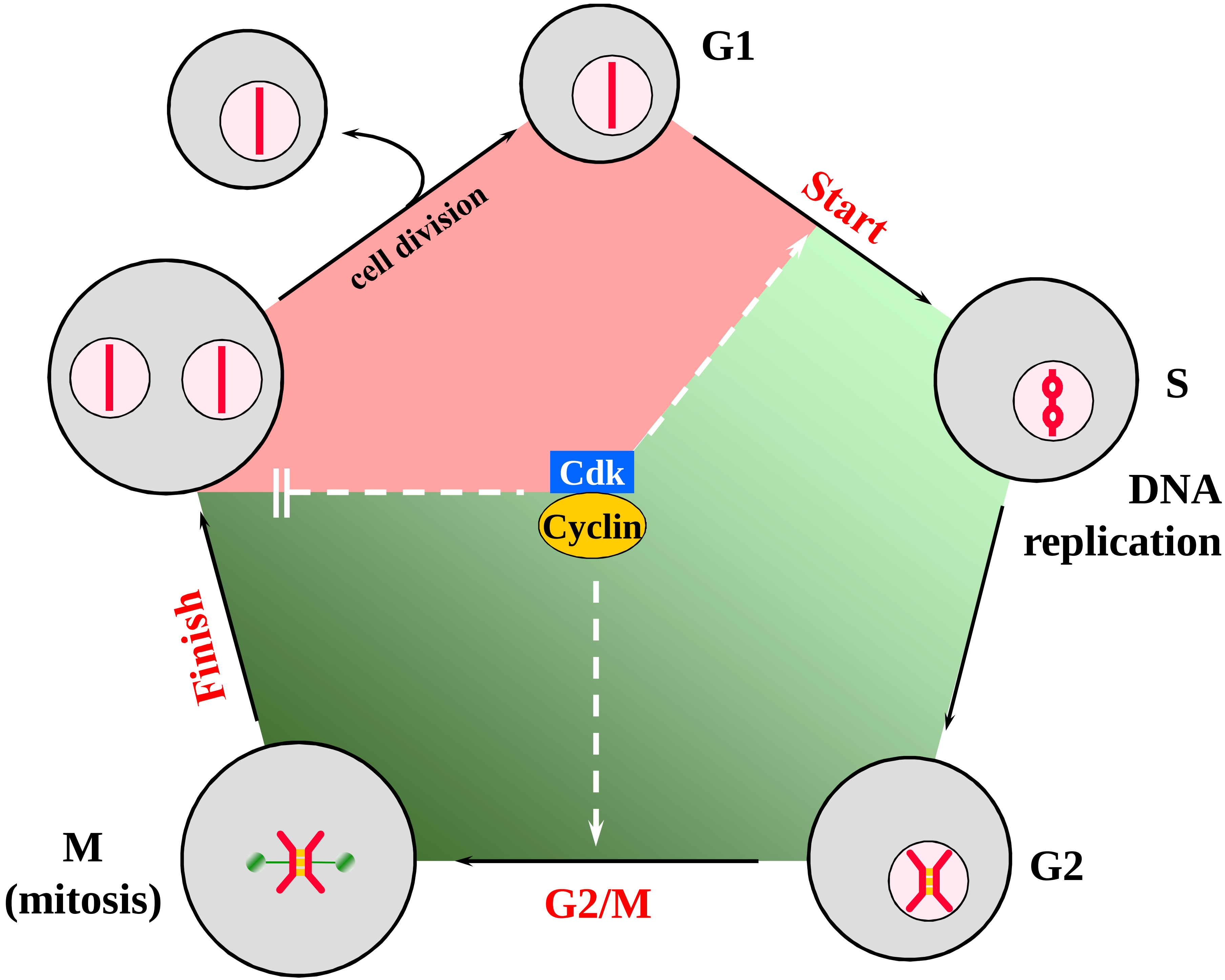
+Cdc2AF
+Wee1-OP11





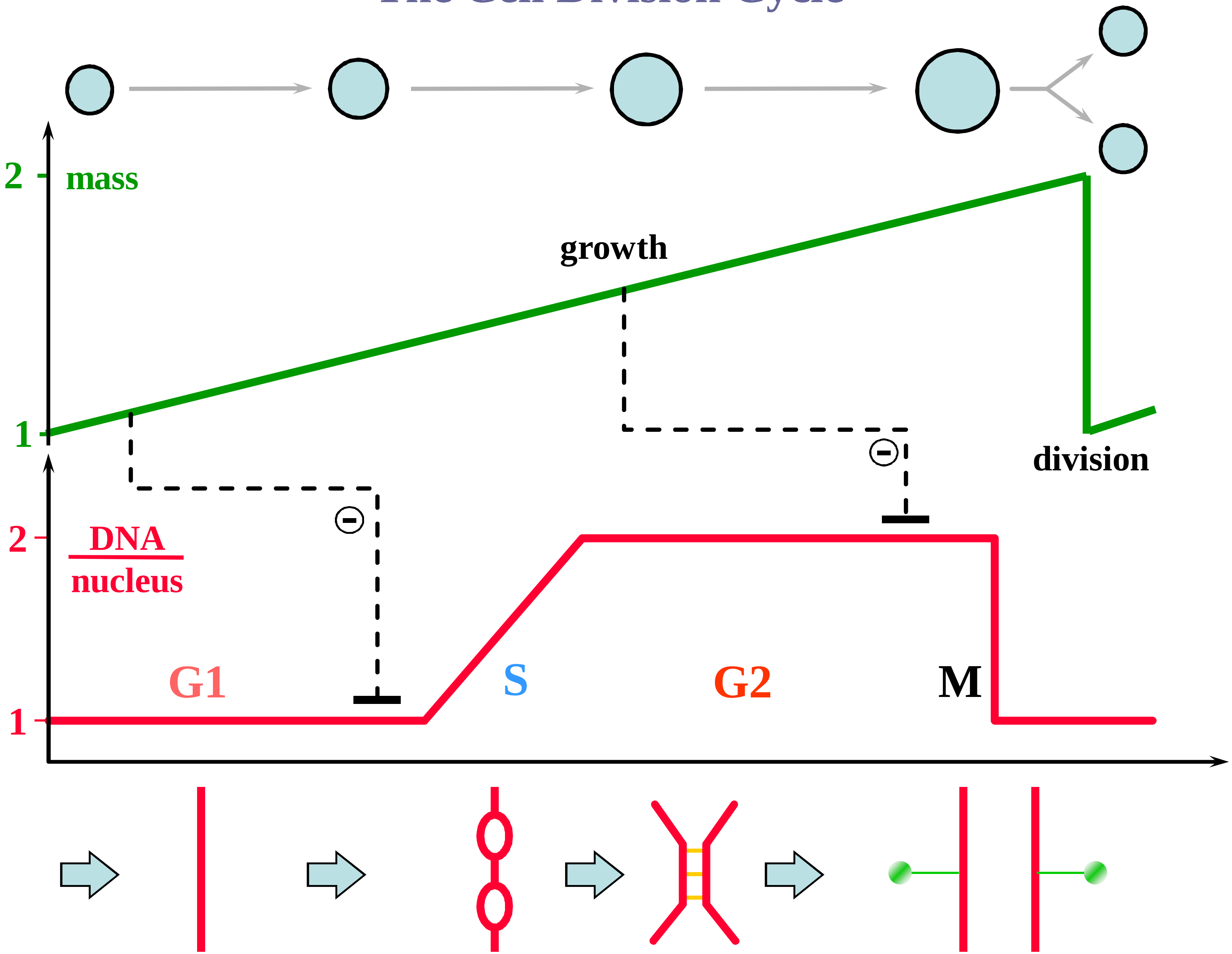
Modeling cell cycle regulation

II. Somatic cycles

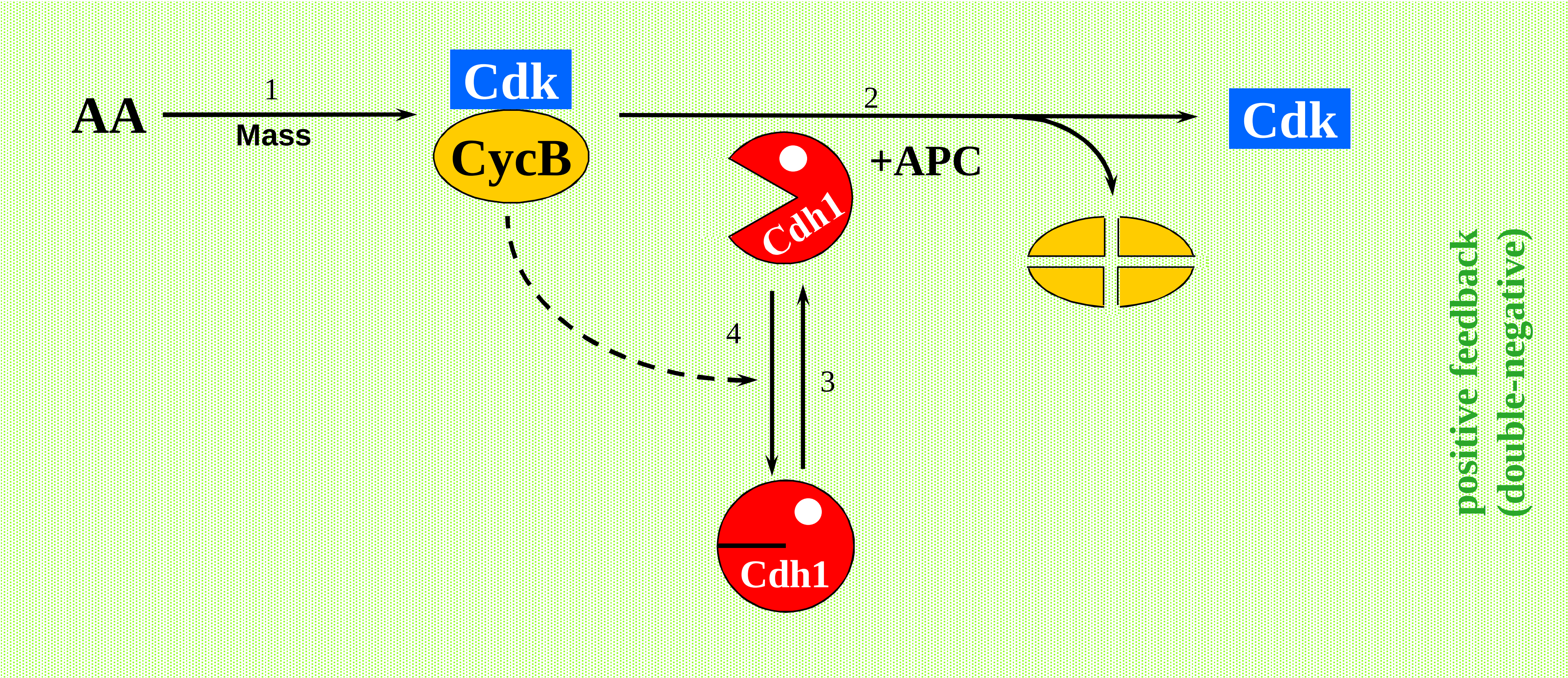


G1
cell division
Start
S
Cdk
Cyclin
DNA
replication
Finish
M
(mitosis)
G2/M
G2

The Cell Division Cycle



Stabilizing the G1 phase

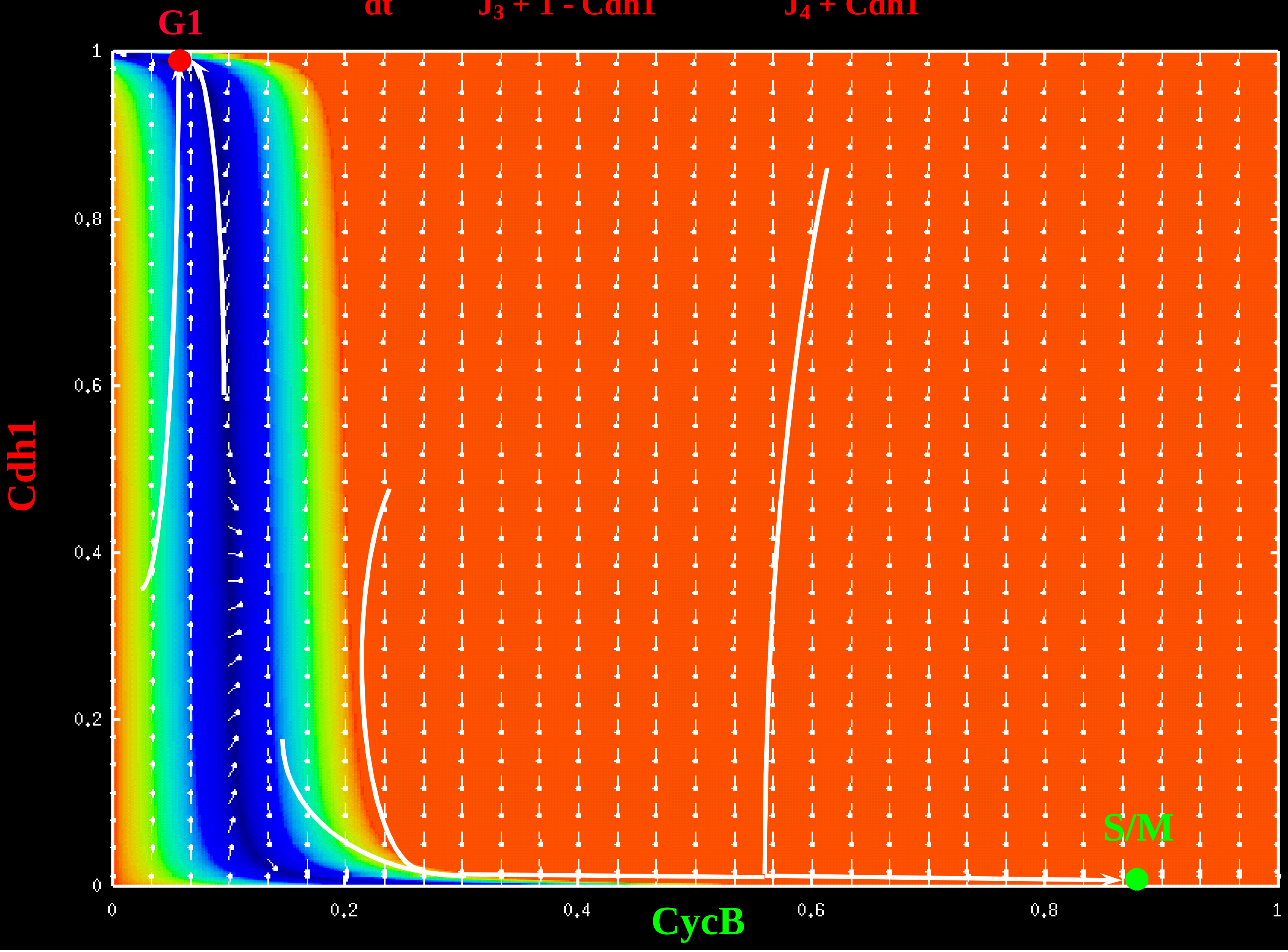


$$\frac{d\,CycB}{dt} = k_1 \cdot M - (k_2' + k_2'' \cdot Cdh1) \cdot CycB$$

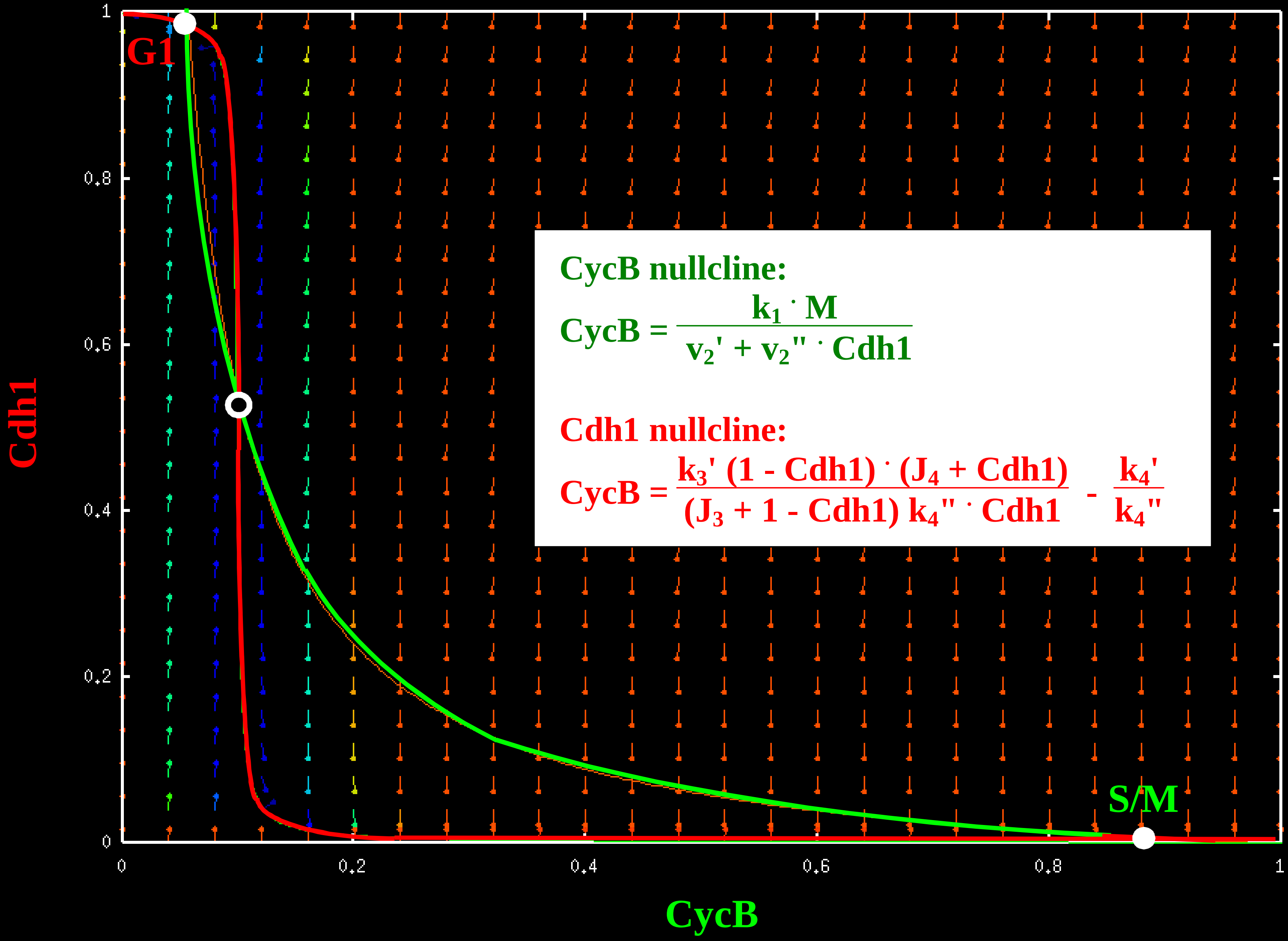
$$\frac{d\,Cdh1}{dt} = \frac{k_3' \cdot (1 - Cdh1)}{J_3 + 1 - Cdh1} - \frac{(k_4' + k_4'' \cdot CycB)\,Cdh1}{J_4 + Cdh1}$$

$$\frac{d\,CycB}{dt} = k_1 \cdot M - (k_2' + k_2'' \cdot Cdh1) \cdot CycB$$

$$\frac{d\,Cdh1}{dt} = \frac{k_3' \cdot (1 - Cdh1)}{J_3 + 1 - Cdh1} - \frac{(k_4' + k_4'' \cdot CycB)\, Cdh1}{J_4 + Cdh1}$$



Nullclines

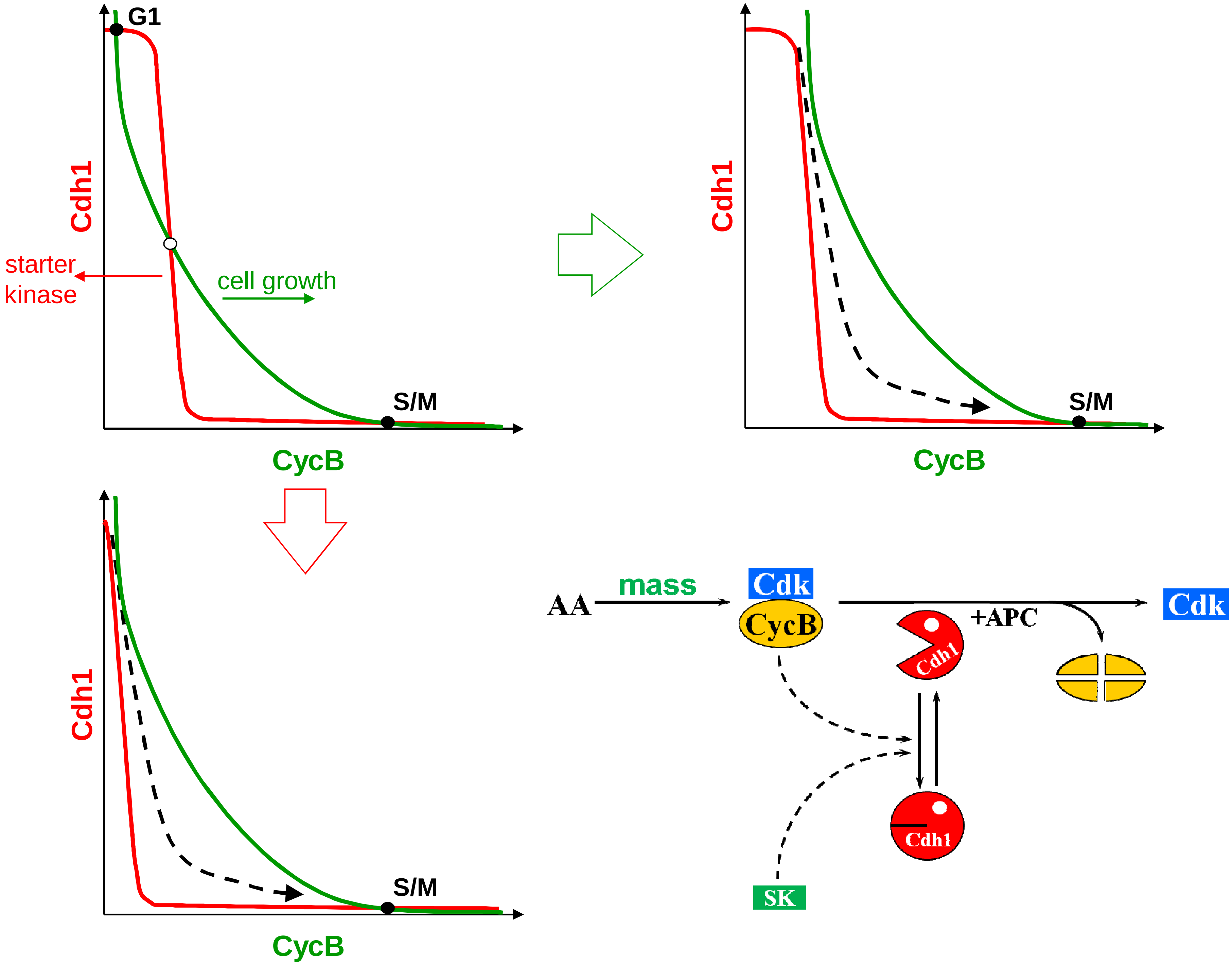


CycB nullcline:

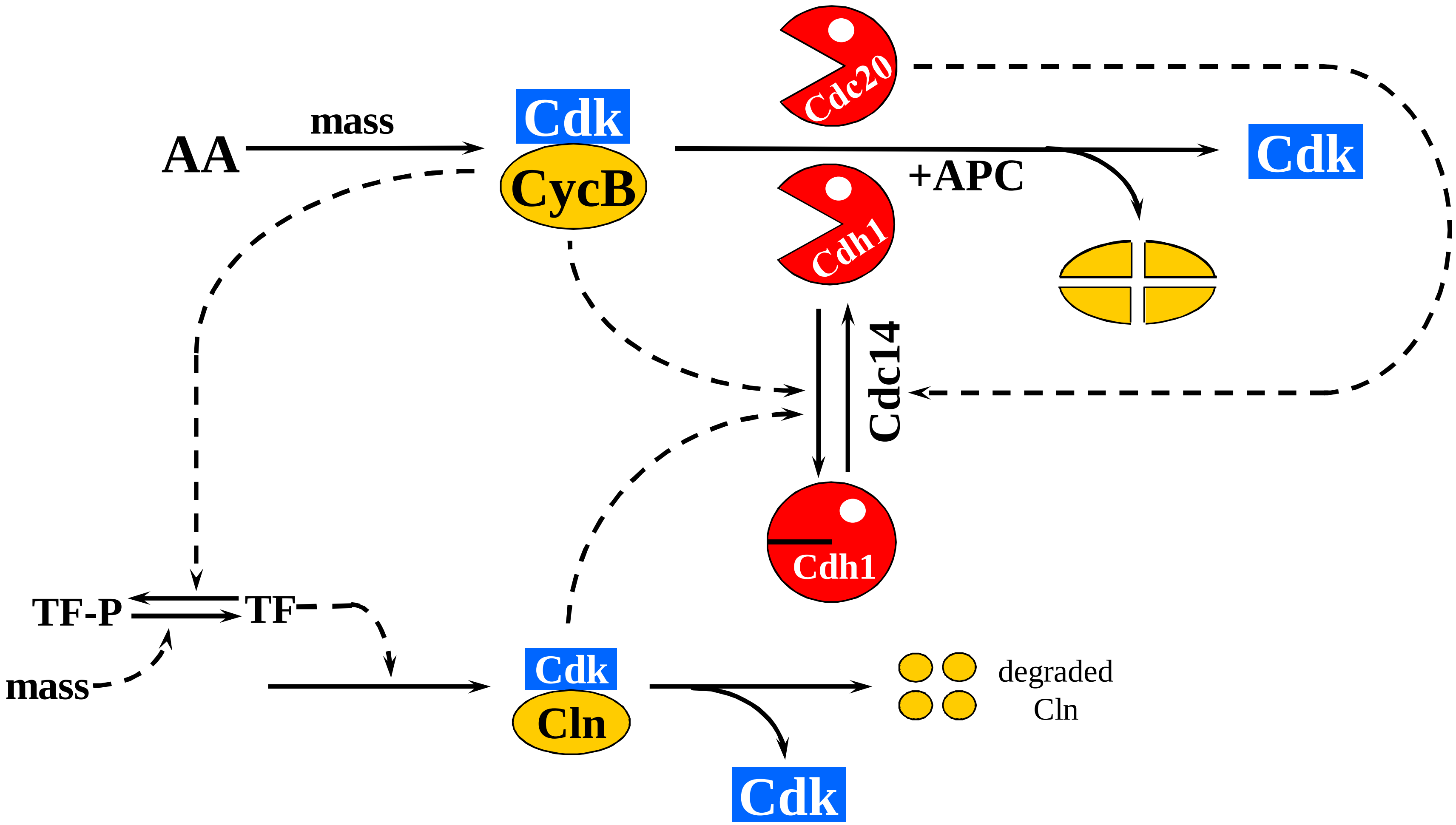
$$CycB = \frac{k_1 \cdot M}{v_2' + v_2'' \cdot Cdh1}$$

Cdh1 nullcline:

$$CycB = \frac{k_3' (1 - Cdh1) \cdot (J_4 + Cdh1)}{(J_3 + 1 - Cdh1)\, k_4'' \cdot Cdh1} - \frac{k_4'}{k_4''}$$


G1
Cdh1
starter
kinase
cell growth
S/M
CycB
Cdh1
S/M
CycB
Cdh1
S/M
CycB
AA
mass
Cdk
CycB
+APC
Cdk
Cdh1
Cdh1
SK

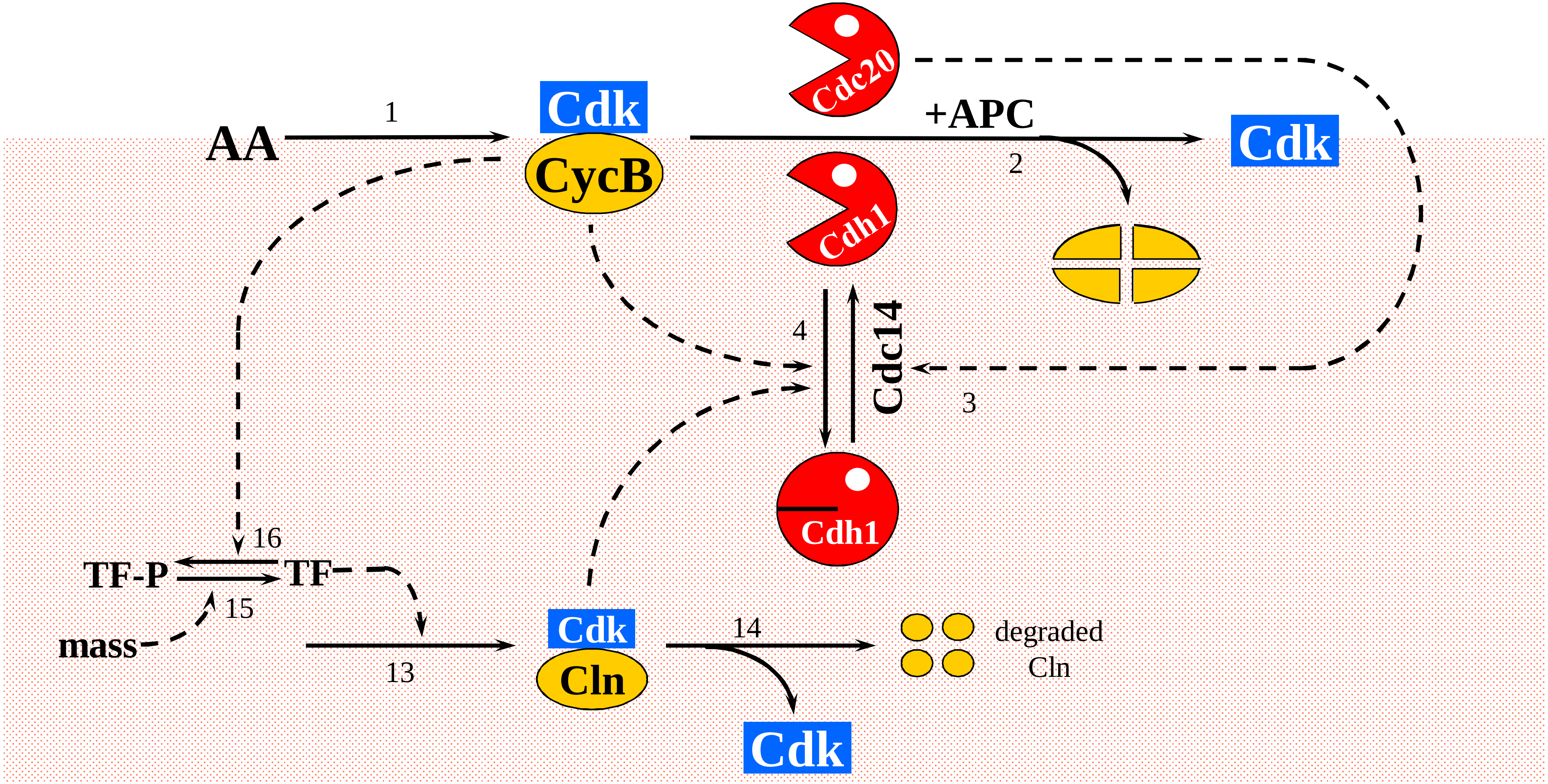
Turning on/off the Cdk - Cdh1 switch

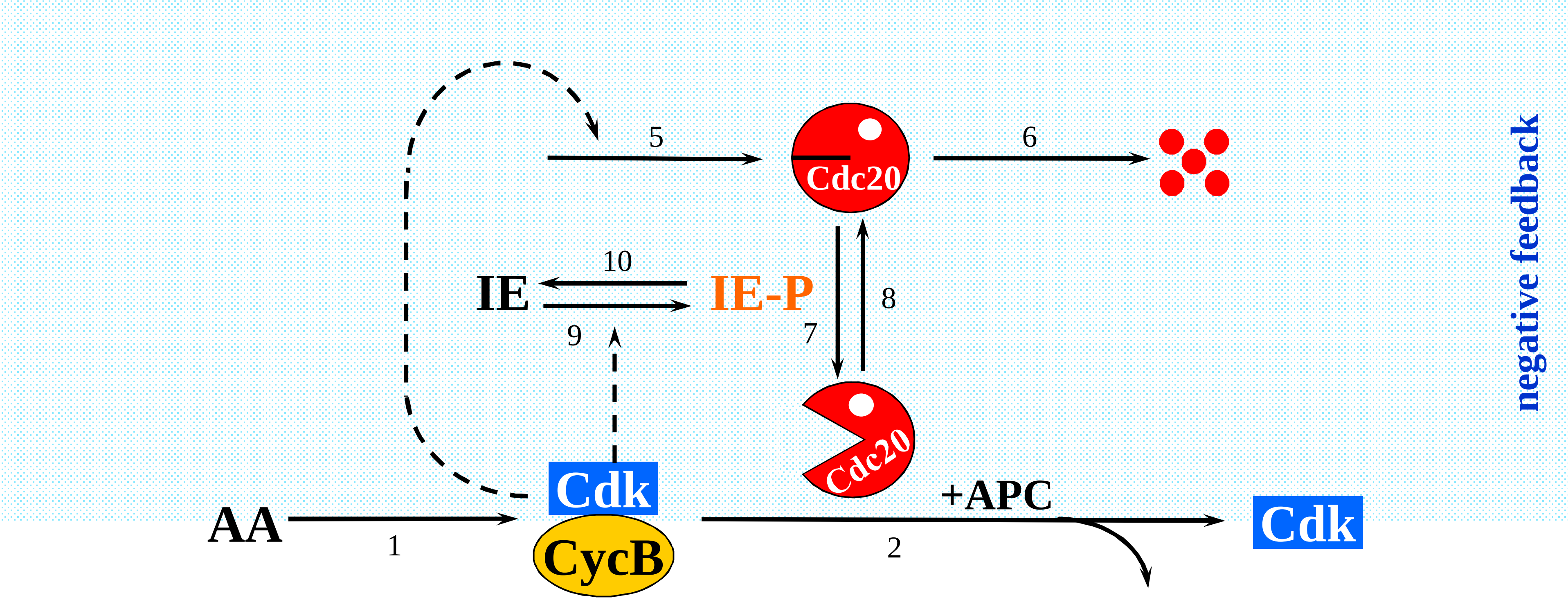


$$\frac{d\,Cdh1}{dt} = (k_3' + k_3'' \cdot Cdc20_A)\frac{1 - Cdh1}{J_3 + 1 - Cdh1} - (k_4' \cdot SK + k_4 \cdot CycB)\frac{Cdh1}{J_4 + Cdh1}$$

$$\frac{d\,SK}{dt} = k_{13}' + k_{13}'' \cdot TF - k_{14} \cdot SK$$

$$\frac{d\,TF}{dt} = k_{15}' \cdot M \frac{1 - TF}{J_{15} + 1 - TF} - (k_{16}' + k_{16}'' \cdot CycB)\frac{TF}{J_{16} + TF}$$





$$\frac{d\,Cdc20_T}{dt} = k_5' + \frac{k_5'' \cdot CycB^4}{J_5^4 + CycB^4} - k_6 \cdot Cdc20_T$$

$$\frac{dCdc20_A}{dt} = k_7 \cdot IE\text{-}P \; \frac{Cdc20_T - Cdc20_A}{J_7 + Cdc20_T - Cdc20_A} - k_8 \cdot \frac{Cdc20_A}{J_8 + Cdc20_A} - k_6 \cdot Cdc20_A$$

$$\frac{d\,IE\text{-}P}{dt} = k_9 \cdot CycB \frac{1 - IE\text{-}P}{J_9 + 1 - IEP} - k_{10} \cdot \frac{IE\text{-}P}{J_{10} + IE\text{-}P}$$

$$\frac{dCycB}{dt} = k_1 \cdot M - (k_2' + k_2'' \cdot Cdh1 + k_2''' \cdot Cdc20_A)\, CycB$$

$$\frac{d\,Cdh1}{dt} = (k_3' + k_3'' \cdot Cdc20_A) \frac{1-Cdh1}{J_3+1-Cdh1} - (k_4' \cdot SK + k_4 \cdot CycB) \frac{Cdh1}{J_4 + Cdh1}$$

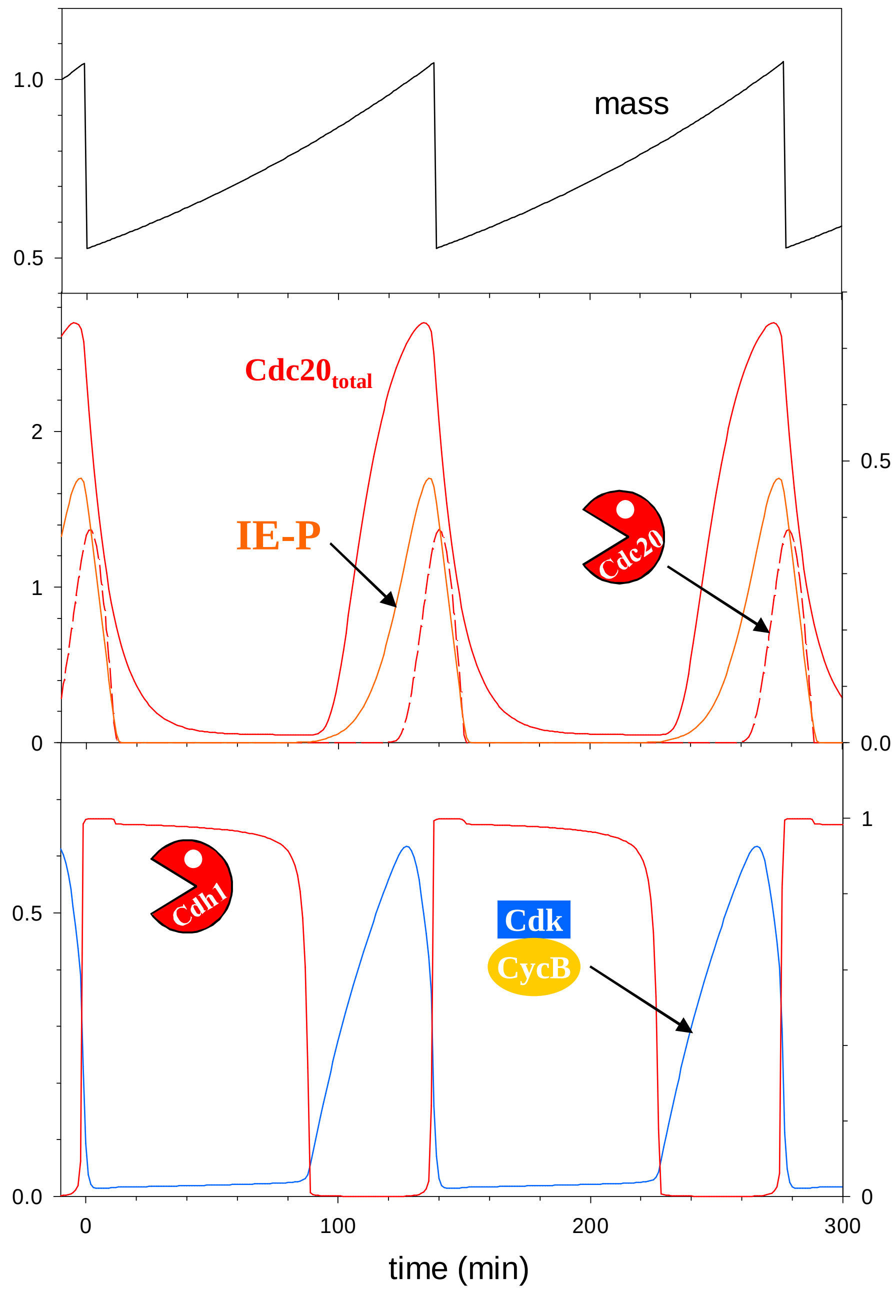
$$\frac{d\,SK}{dt} = k_{13}' + k_{13}'' \cdot TF - k_{14} \cdot SK$$

$$\frac{d\,TF}{dt} = k_{15}' \cdot M \frac{1 - TF}{J_{15} + 1 - TF} - (k_{16}' + k_{16}'' \cdot CycB) \frac{TF}{J_{16} + TF}$$

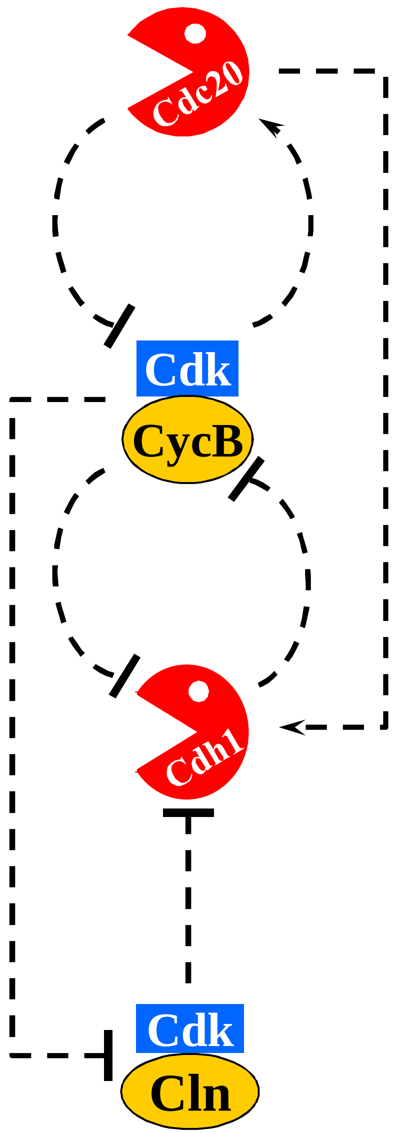
$$\frac{d\,Cdc20_T}{dt} = k_5' + \frac{k_5'' \cdot CycB^4}{J_5^4 + CycB^4} - k_6 \cdot Cdc20_T$$

$$\frac{dCdc20_A}{dt} = k_7 \cdot IE\text{-}P \frac{Cdc20_T - Cdc20_A}{J_7 + Cdc20_T - Cdc20_A} - k_8 \cdot \frac{Cdc20_A}{J_8 + Cdc20_A} - k_6 \cdot Cdc20_A$$

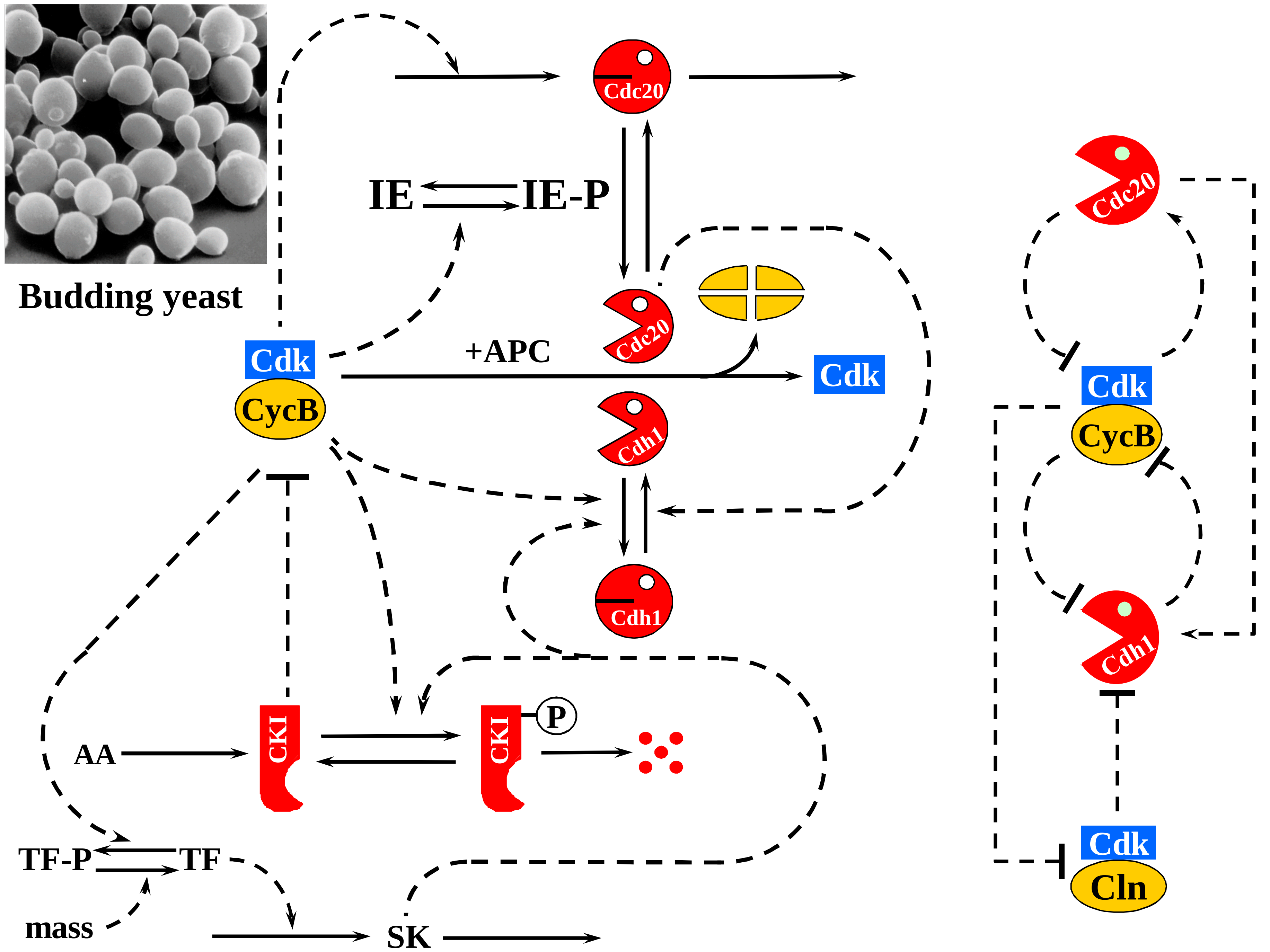
$$\frac{d\,IE\text{-}P}{dt} = k_9 \cdot CycB \frac{1 - IE\text{-}P}{J_9 + 1 - IE\text{-}P} - k_{10} \cdot \frac{IE\text{-}P}{J_{10} + IE\text{-}P}$$

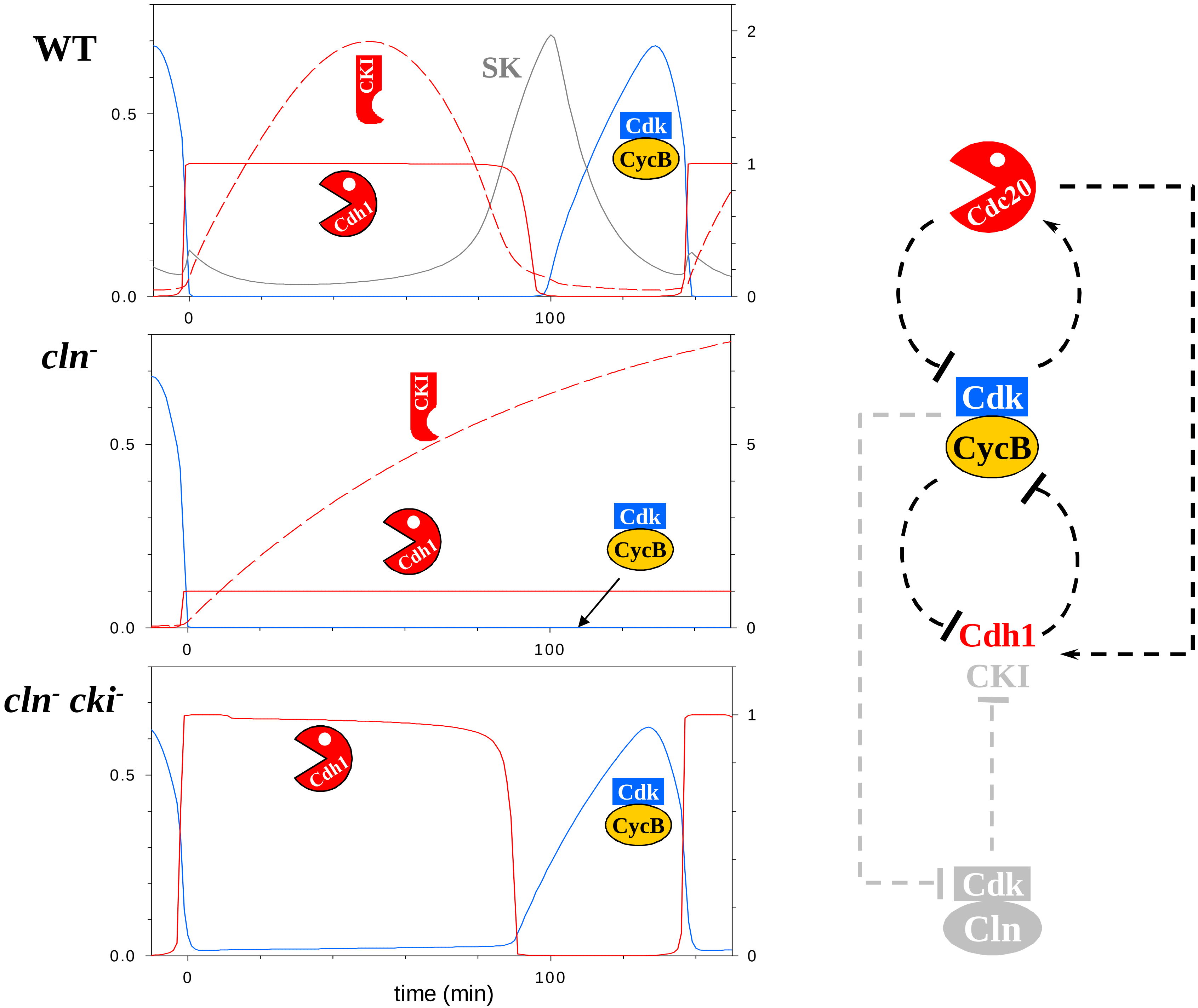


mass
1.0
0.5
Cdc20total
IE-P
Cdc20
2
1
0
0.5
0.0
Cdh1
Cdk
CycB
0.5
0.0
1
0
0
100
200
300
time (min)



Cdc20
Cdk
CycB
Cdh1
Cdk
Cln


Budding yeast
Cdc20
IE
IE-P
Cdc20
Cdk
CycB
+APC
Cdk
Cdh1
Cdh1
AA
CKI
CKI
P
TF-P
TF
mass
SK
Cdc20
Cdk
CycB
Cdh1
Cdk
Cln



WT
SK
CKI
Cdh1
Cdk
CycB
0.5
0.0
0
100
2
1
0
cln-
5
cln- cki-
time (min)
Cdc20
Cdk
CycB
Cdh1
CKI
Cdk
Cln

What makes us believe that our set of equations and parameters are close to life?

Test the model! Compare the results to life:

What can be easy to measure?

- Length of different cell cycle phases
- Cell size at different transitions

Not only wild type, but many mutants!

One wild type parameter set. To simulate mutants use this as a basal parameter set.

Molecular Biology of the Cell
Vol. 15, 3841–3862, August 2004

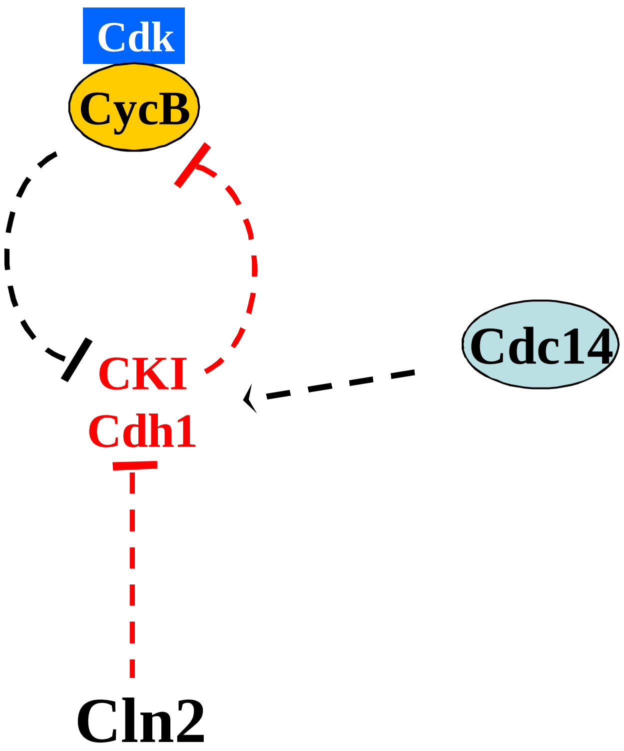
Integrative Analysis of Cell Cycle Control in Budding Yeast D

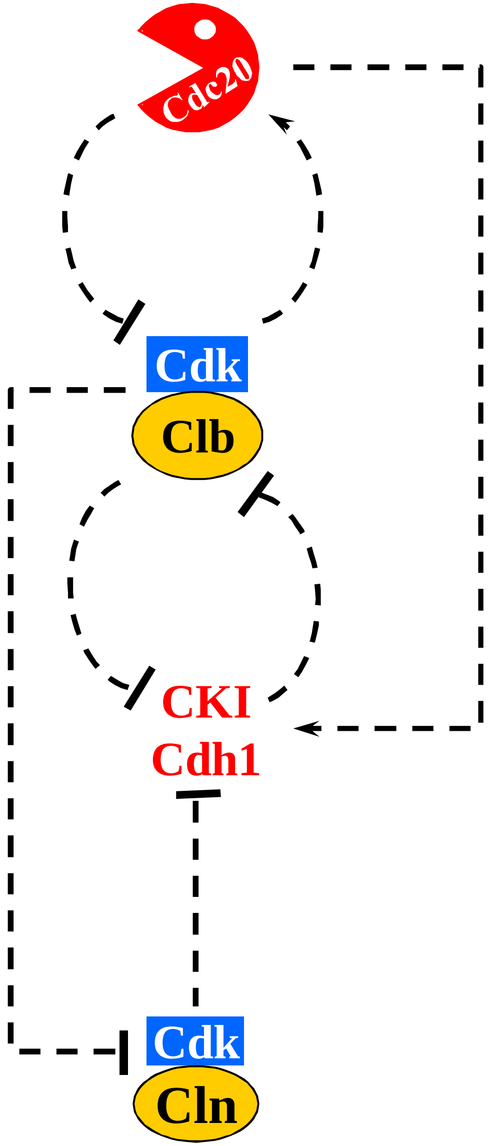
Katherine C. Chen,*† Laurence Calzone,* Attila Csikasz-Nagy,‡ Frederick R. Cross,§ Bela Novak,‡ and John J. Tyson*†

						...e at ...sion	T_{G1} (min)	Changed parameter	Comments (Experimental results in boldface type)
						...4 (...6′)	84		CT 146 min (time of occurrence of event)
						...11]		$D_{n3}=0$ $k''_{s,n2}=0$	**Richardson, 1989, inviable**
						...50	25	$D_{n3}=20$ $k''_{s,n2}=0$	**Schwob, 1993, Fig. 2, SBF activated soon after galactose induction**
						...79	25	$D_{n3}=0$ $k'_{s,n2}=0.1$ $k''_{s,n2}=0$	**Cross, 1991, Fig. 4, *GAL-CLN1* induces *cln2***
						...52	98	$D_{n3}=k''_{s,n2}=0$ $k'_{s,b5}=0.012$ $k''_{s,b5}=0.04$	**Epstein, 1992, viable**
	GAL-CLB5					...86	88	$D_{n3}=k''_{s,n2}=0$ $k'_{s,b5}=0.1$ $k''_{s,b5}=0$	**Schwob, 1993, Fig. 6, viable**
7	*cln1 cln2 cln3 GAL-CLB2*	0.71	2.57	[5.49]	[6.64]	[7.38]		$D_{n3}=k''_{s,n2}=0$ $k'_{s,b2}=0.1$ $k''_{s,b2}=0$	**Amon, 1994, Fig. 8, G1 arrest** We consider cells arrested in G1 if mass at DNA replication exceeds 5
8	*cln1 cln2 cln3 sic1*	1.30	2.12 (85′)	1.50 (24′)	2.24 (94′)	3.01 (146′)	24	$D_{n3}=k''_{s,n2}=0$ $k'_{s,c1}=0$ $k''_{s,c1}=0$	**Tyers, 1996, Fig. 2, viable but large**
9	*cln1 cln2 cln3 hct1*	0.71	2.48	4.62	5.03	No mit		$D_{n3}=k''_{s,n2}=0$ $k''_{d,b2}=0.01$	**Schwab, 1997, Fig. 3, M phase arrest**
10	*cln1 cln2 cln3 apc-ts*	0.71	2.48	4.16	4.60	No mit		$D_{n3}=k''_{s,n2}=0$ $k''_{d,b2}=0.01$ $k'''_{d,b2}=0$ $k''_{d,b5}=0$	**Irniger, 1997, Fig. 2, M phase arrest**

Current Budding yeast model 131 mutants
Current Fission yeast model 59 mutants

Hysteresis in budding yeast cell cycle?

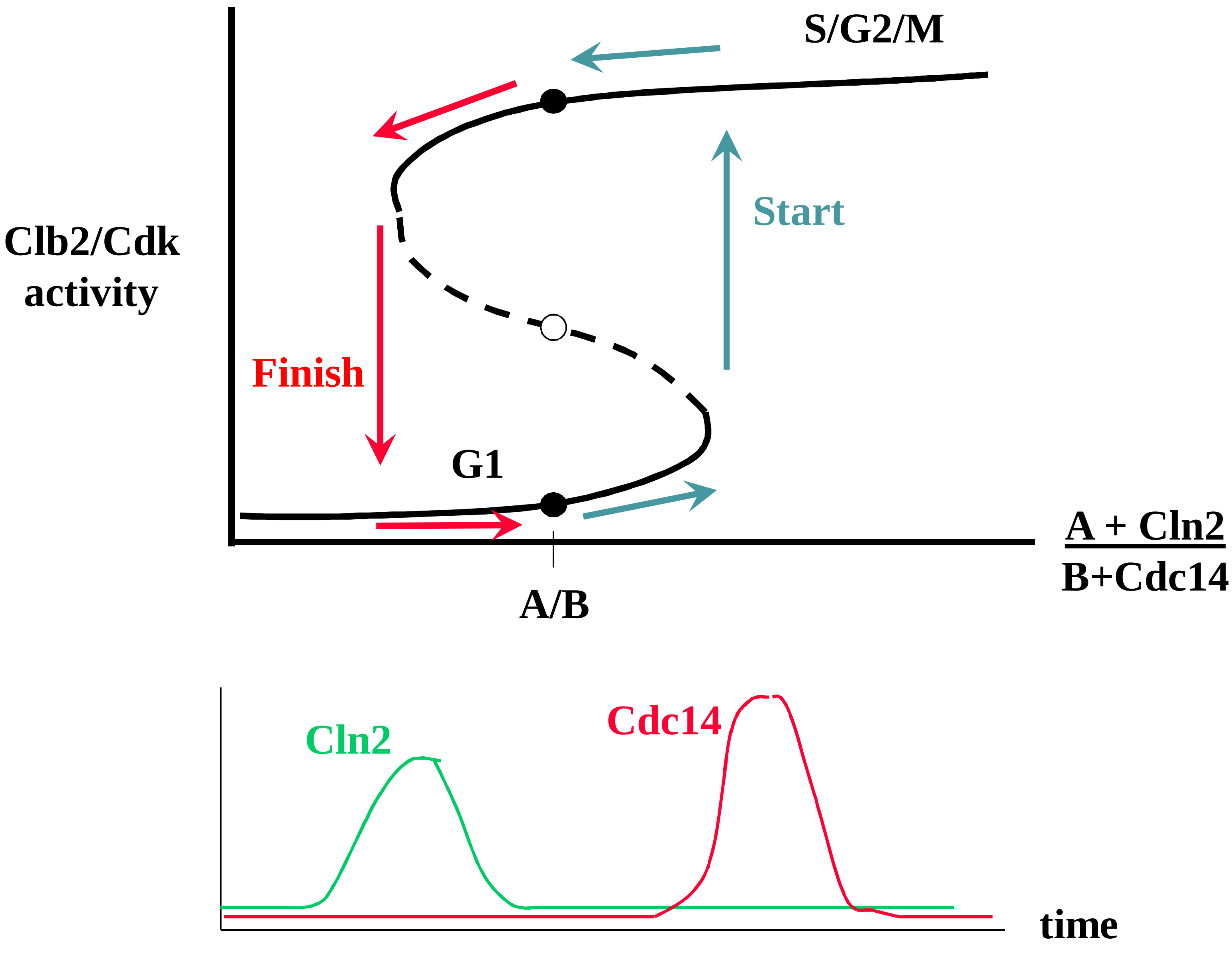


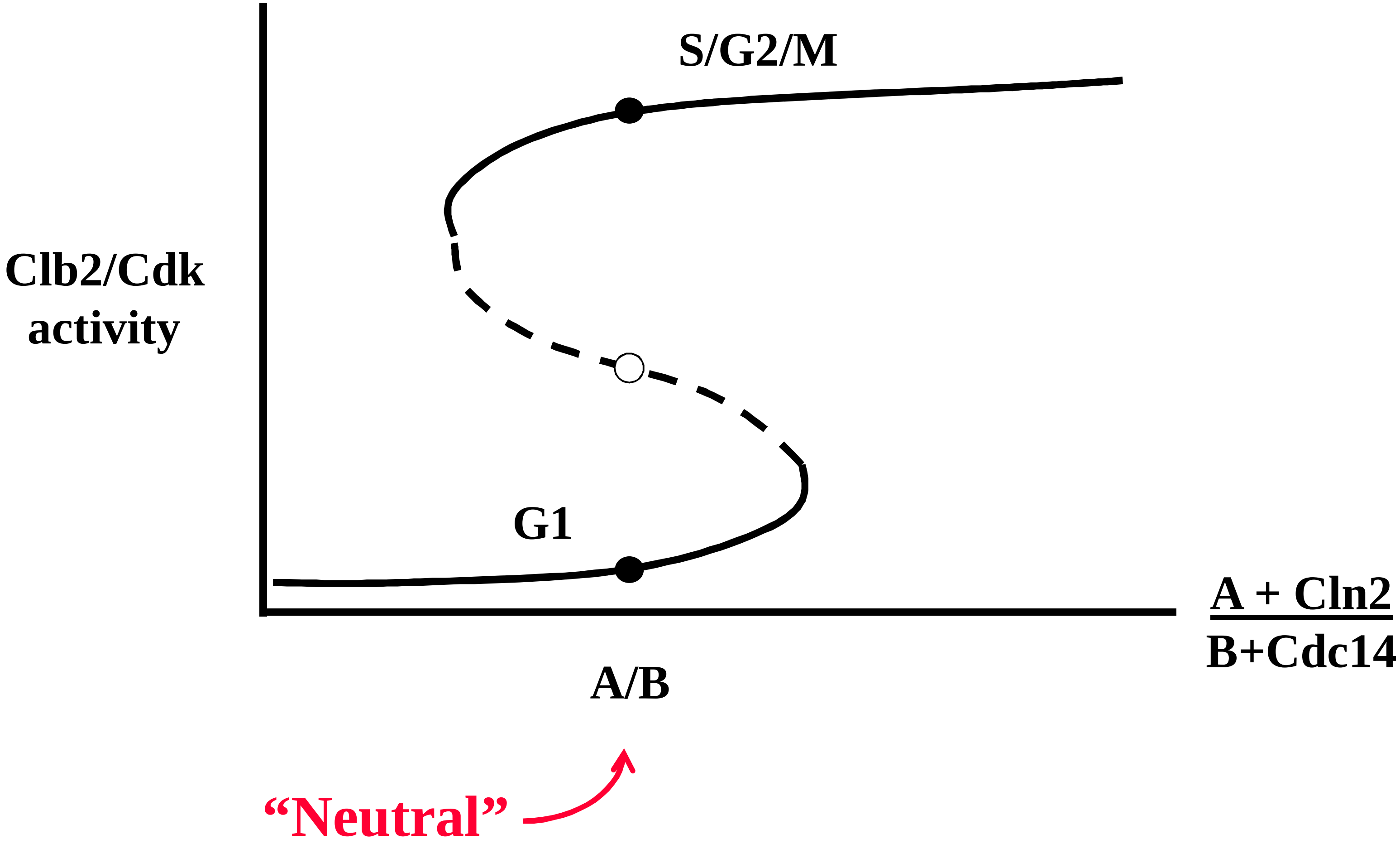


Molecular Biology of the Cell
Vol. 11, 369–391, January 2000

Kinetic Analysis of a Molecular Model of the Budding Yeast Cell Cycle

Katherine C. Chen,* Attila Csikasz-Nagy,† Bela Gyorffy,† John Val,*
Bela Novak,† and John J. Tyson*‡


S/G2/M
Start
Clb2/Cdk
activity
Finish
G1
A + Cln2
B+Cdc14
A/B
Cdc14
Cln2
time


S/G2/M
Clb2/Cdk
activity
G1
A + Cln2
B+Cdc14
A/B
"Neutral"

Protocol to demonstrate hysteresis

Fred Cross

Genotype: *cln1Δ cln2Δ cln3Δ GAL-CLN3 cdc14*^{ts}

Knockout all the G1cyclins

Turn on *CLN3* with galactose; turn off with glucose

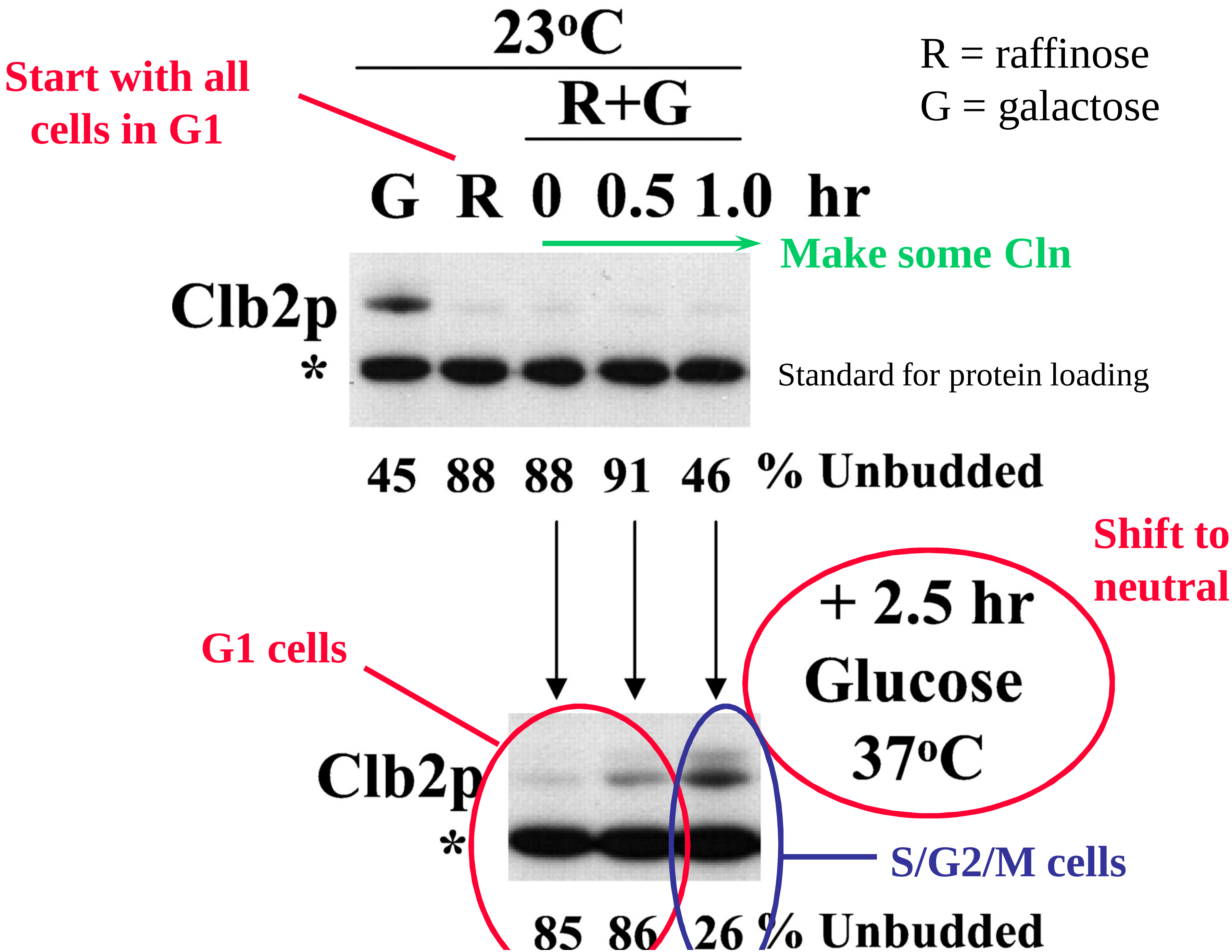
Temperature-sensitive allele of *CDC14*: on at 23^{o}C, off at 37^{o}C.

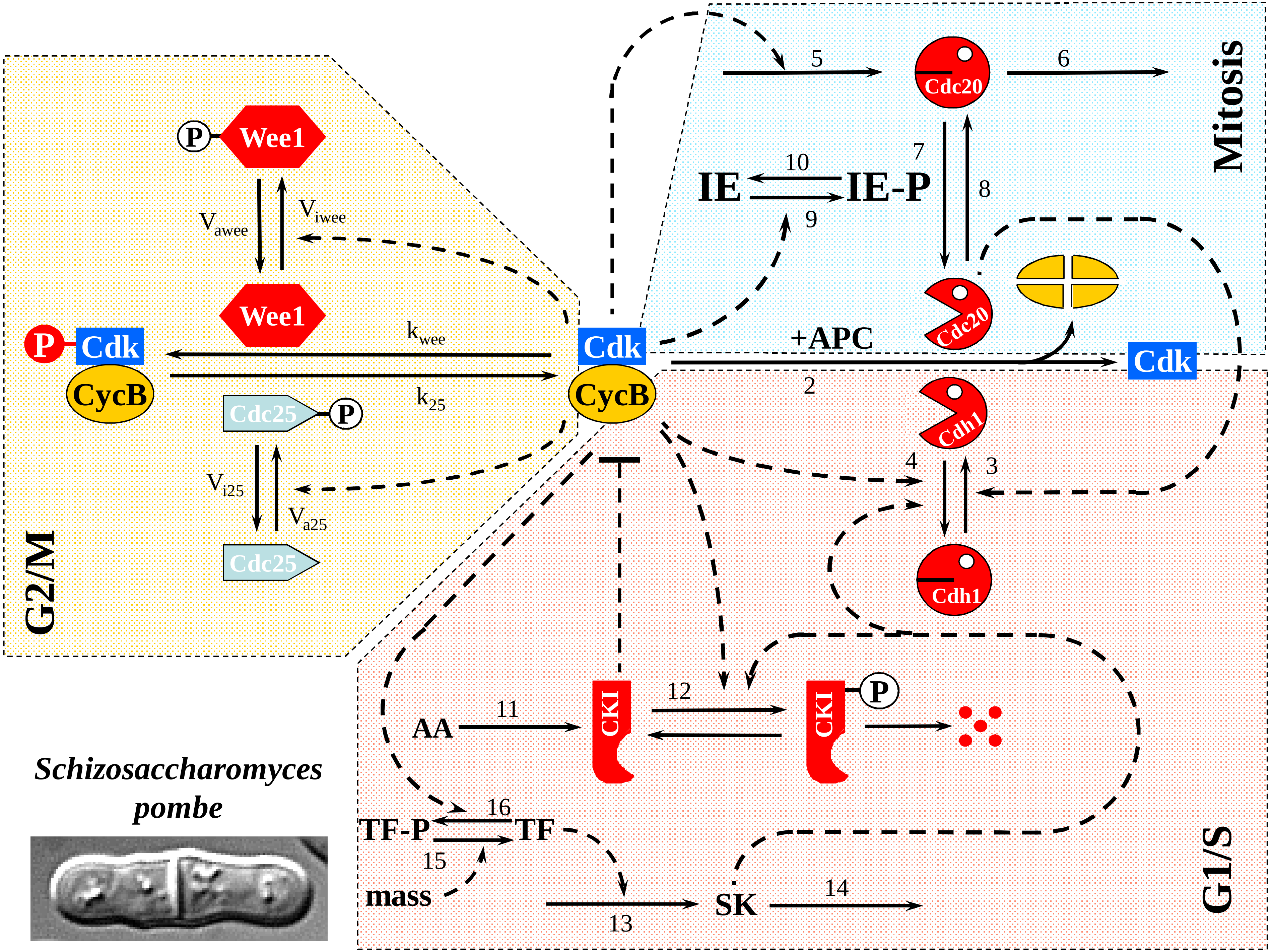
"Neutral" conditions: glucose at 37^{o}C (no Cln's, no Cdc14)

Molecular Biology of the Cell
Vol. 13, 52–70, January 2002

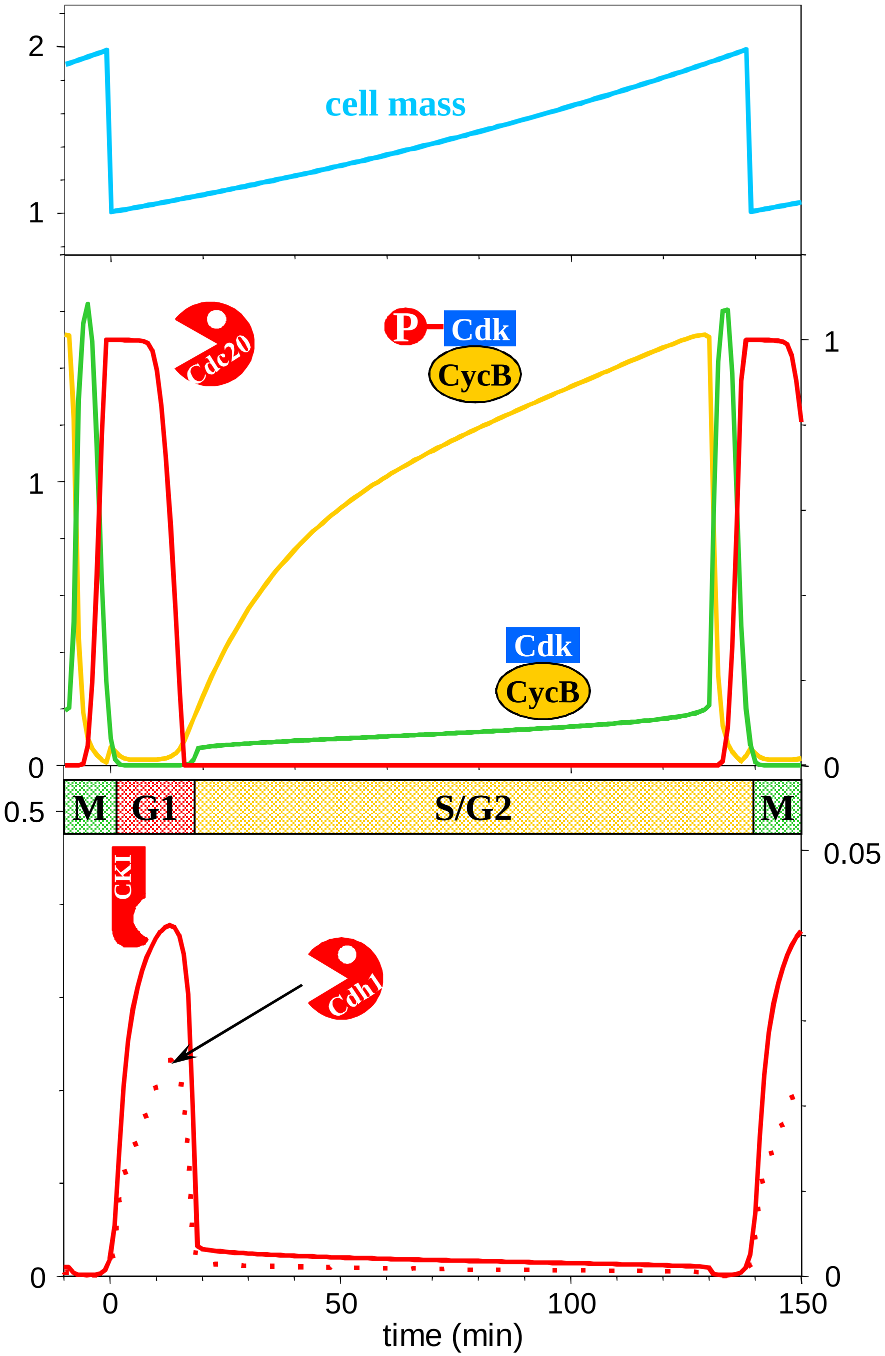
Testing a Mathematical Model of the Yeast Cell Cycle

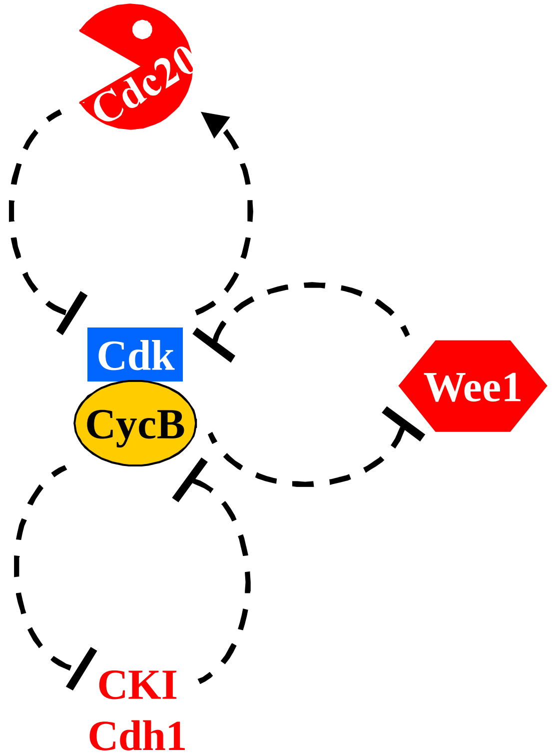
Frederick R. Cross,* Vincent Archambault, Mary Miller, and Martha Klovstad

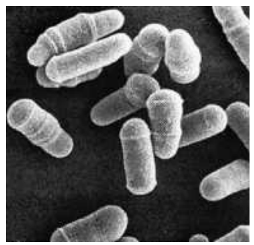

23°C
R+G
R = raffinose
G = galactose
Start with all cells in G1
G R 0 0.5 1.0 hr
Make some Cln
Clb2p
*
Standard for protein loading
45 88 88 91 46 % Unbudded
Shift to neutral
+ 2.5 hr
Glucose
37°C
G1 cells
Clb2p
*
S/G2/M cells
85 86 26 % Unbudded



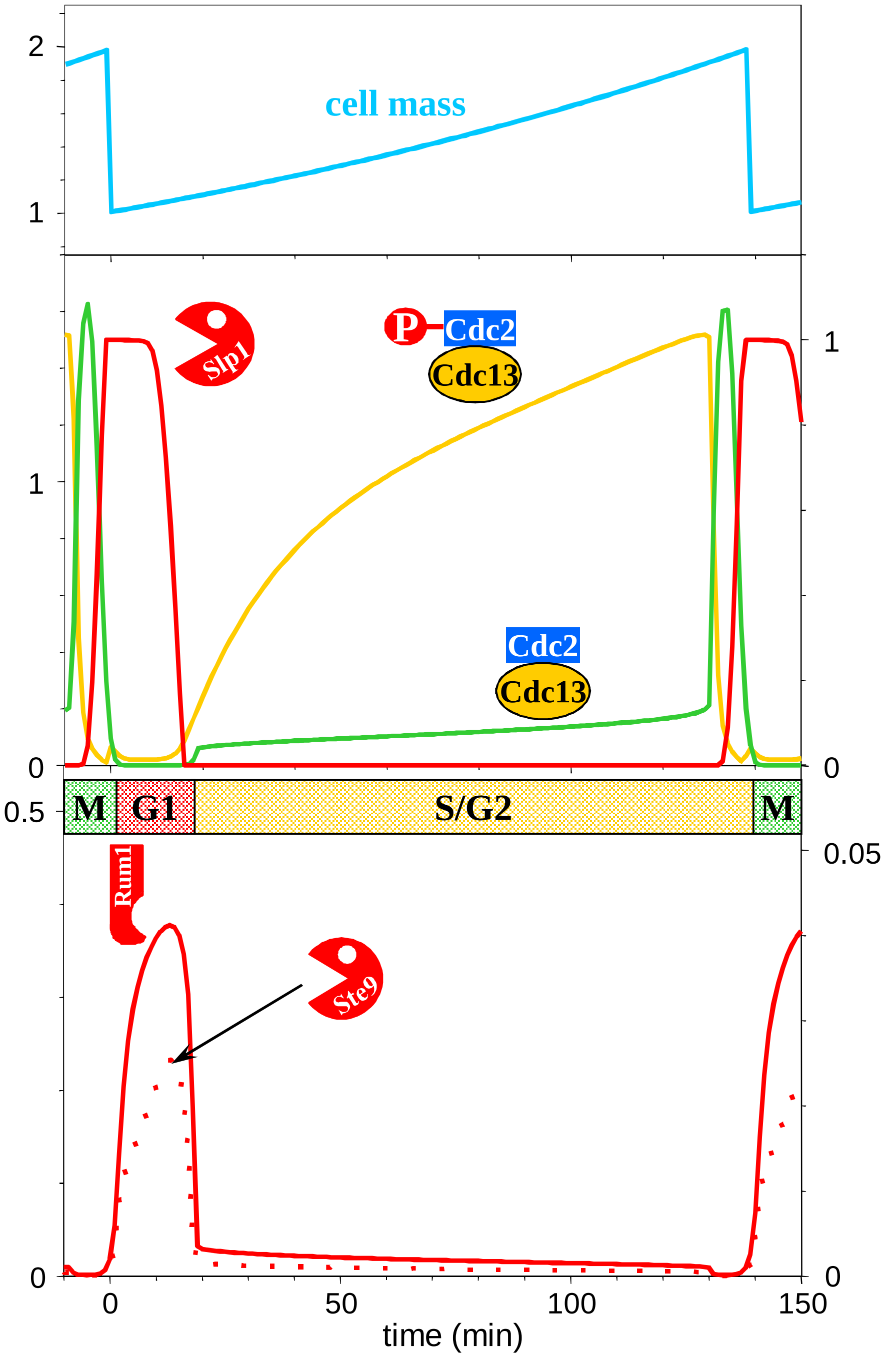
Mitosis
G2/M
G1/S
Wee1
P
Wee1
V_awee
V_iwee
P
Cdk
CycB
k_wee
k_25
Cdk
CycB
Cdc25
P
Cdc25
V_i25
V_a25
5
6
Cdc20
7
8
10
IE
IE-P
9
Cdc20
+APC
Cdk
2
Cdh1
4
3
Cdh1
11
AA
CKI
12
CKI
P
16
TF-P
TF
15
mass
13
SK
14
Schizosaccharomyces pombe

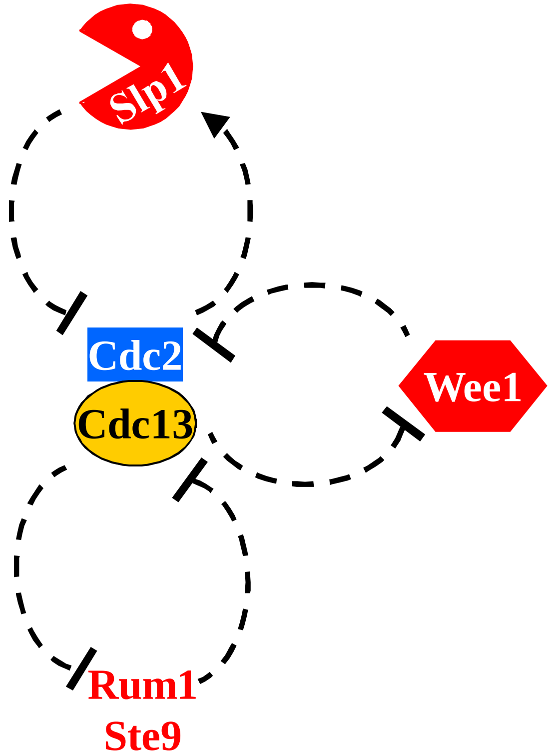


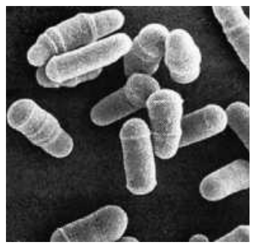




Fission yeast







Fission yeast

Bifurcation diagram for cell cycle regulation
(*Signal – response curve*)

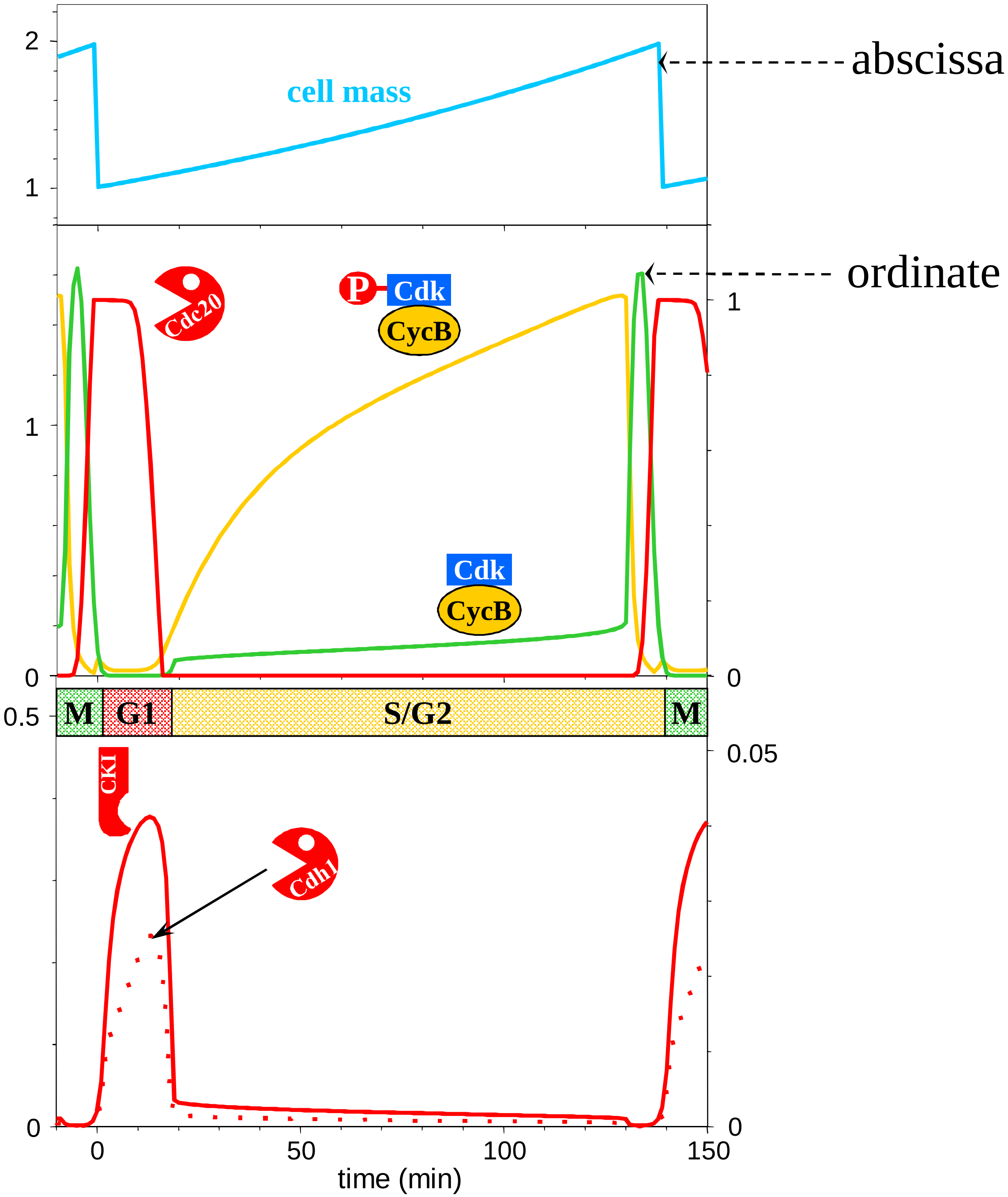
<u>Bifurcation parameter (signal):</u>

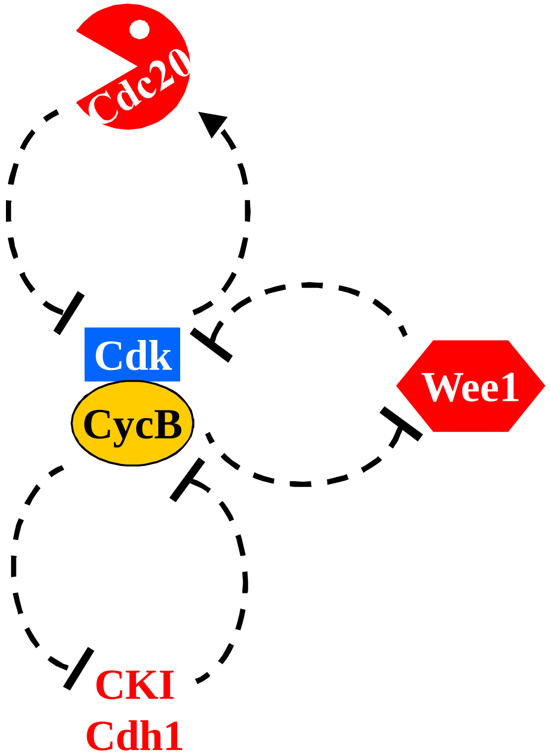
cell mass

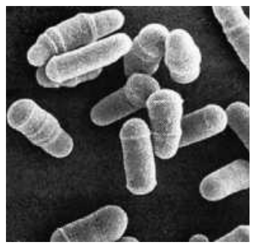
(reports environmental conditions)

<u>State variable (response):</u>

main controller of the system =







Fission yeast

$$\frac{dCycB_T}{dt} = k_1 \cdot \text{cell mass} - (k_2' + k_2'' \cdot Cdh1 + k_2''' \cdot Cdc20_A) \cdot CycB_T$$

$$\frac{dpMPF}{dt} = k_{wee} \cdot (CycB_T - pMPF) - k_{25} \cdot pMPF - (k_2' + k_2'' \cdot Cdh1 + k_2''' \cdot Cdc20_A) \cdot pMPF$$

$$\frac{dIE}{dt} = k_9 \cdot MPF \cdot \frac{1 - IE}{J_9 + 1 - IE} - k_{10} \cdot \frac{IE}{J_{10} + IE}$$

$$\frac{dCdc20}{dt} = k_7 \cdot IE \cdot \frac{1 - Cdc20}{J_7 + 1 - Cdc20} - k_8 \cdot \frac{Cdc20}{J_8 + Cdc20} - k_6 \cdot Cdc20$$

$$\frac{dCdh1}{dt} = k_3' \cdot \frac{1 - Cdh1}{J_3 + 1 - Cdh1} - (k_4' \cdot SK + k_4 \cdot MPF) \cdot \frac{Cdh1}{J_4 + Cdh1}$$

$$\frac{dCKI_T}{dt} = k_{11} - (k_{12} + k_{12}' \cdot SK + k_{12}'' \cdot MPF) \cdot CKI_T$$

$$\frac{dSK}{dt} = k_{13}' + k_{13}'' \cdot M - k_{14} \cdot SK$$

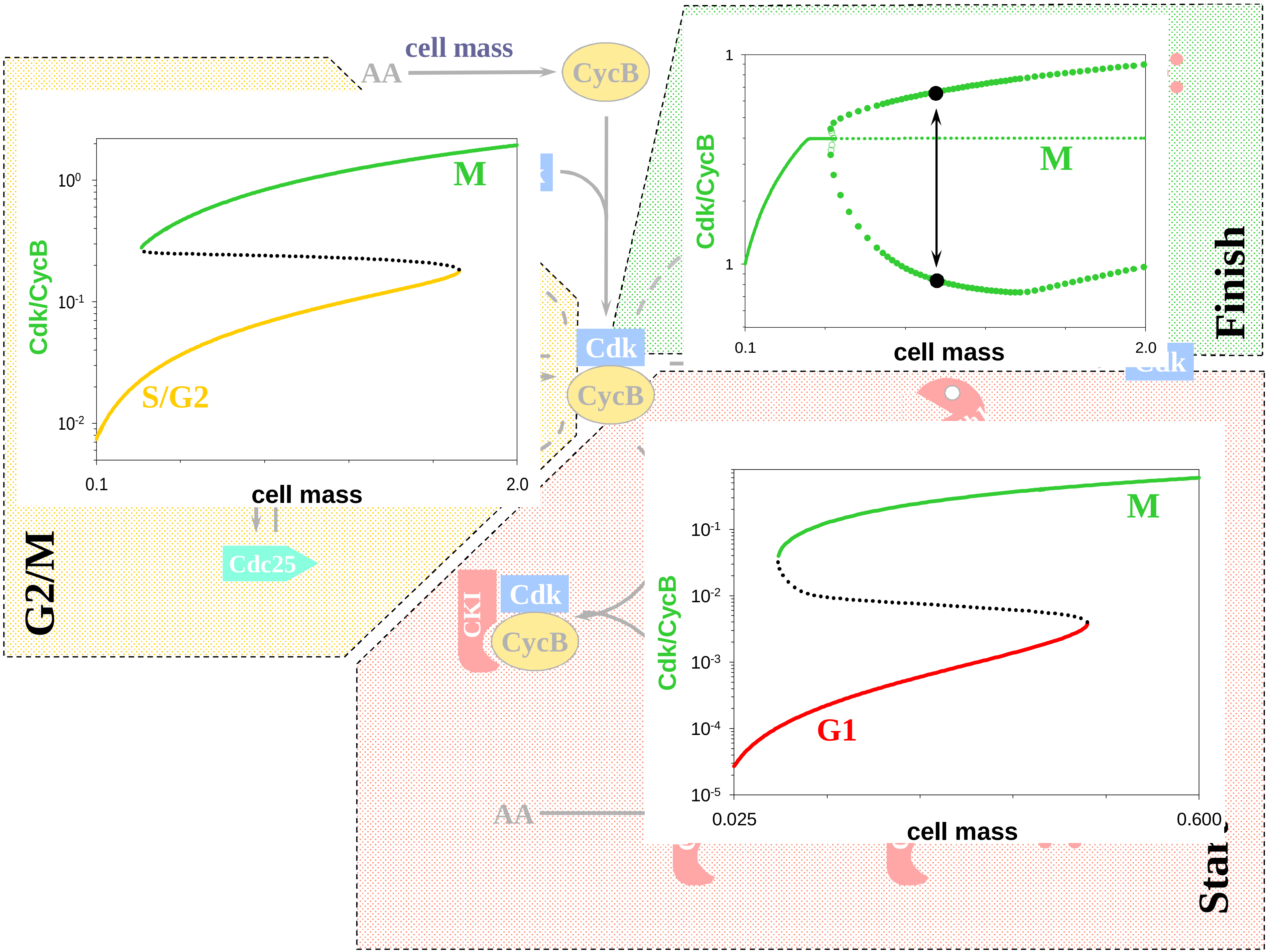
$$\frac{dM}{dt} = \mu \cdot M$$

$$[Trimer] = \frac{2\,[CycB_T]\,[CKI_T]}{[CycB_T] + [CKI_T] + K_{eq}^{-1} + \sqrt{([CycB_T] + [CKI_T] + K_{eq}^{-1})^2 - 4\,[CycB_T]\,[CKI_T]}}$$

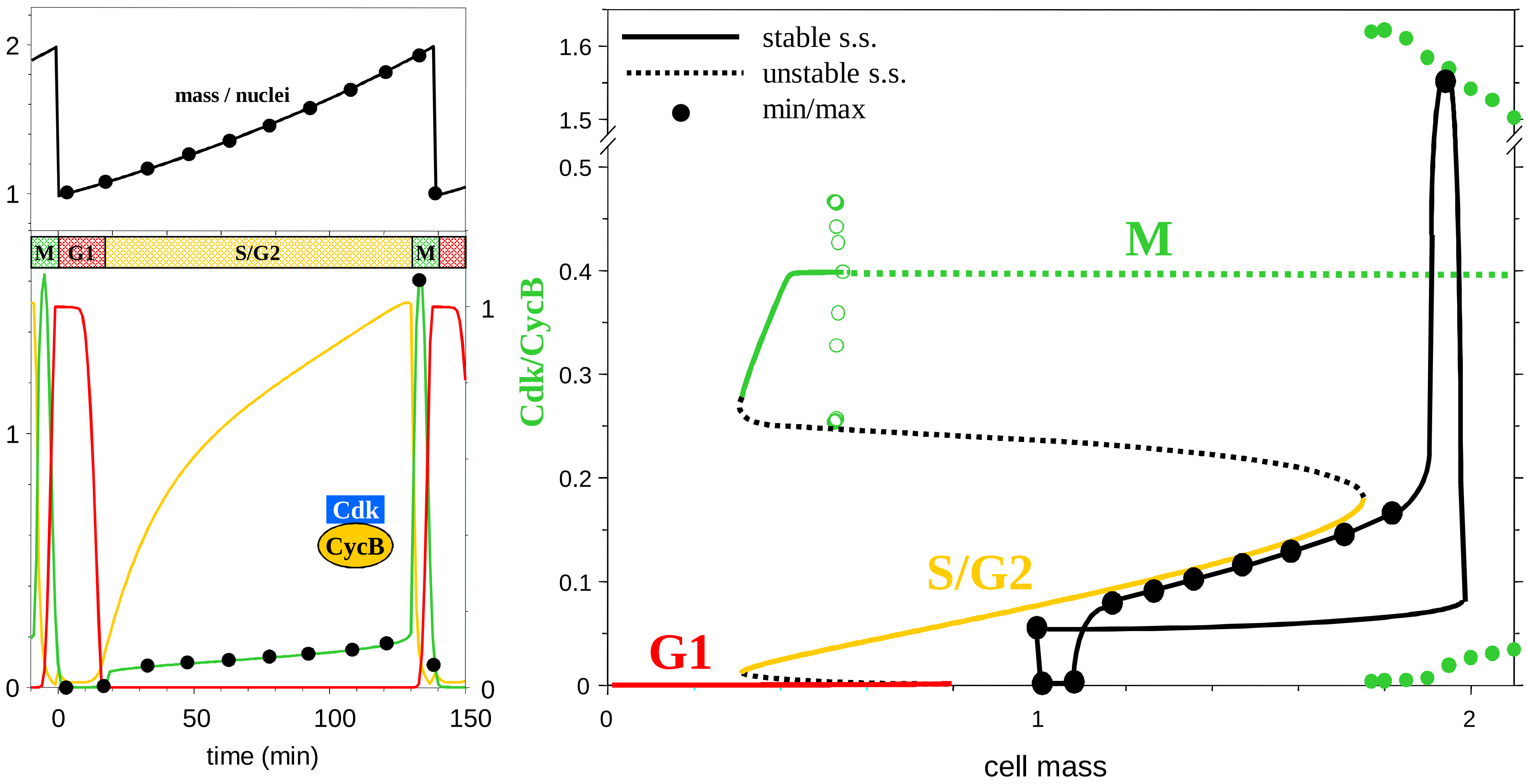
$$k_{wee} = k_{wee}' + (k_{wee}'' - k_{wee}') \cdot GK(V_{awee}, V_{iwee}' + V_{iwee}'' \cdot MPF, J_{awee}, J_{iwee})$$

$$k_{25} = k_{25}' + (k_{25}'' - k_{25}') \cdot GK(V_{a25}' + V_{a25}'' \cdot MPF, V_{i25}, J_{a25}, J_{i25})$$

$$MPF = \frac{(CycB_T - pMPF) \cdot (CycB_T - Trimer)}{CycB_T}$$

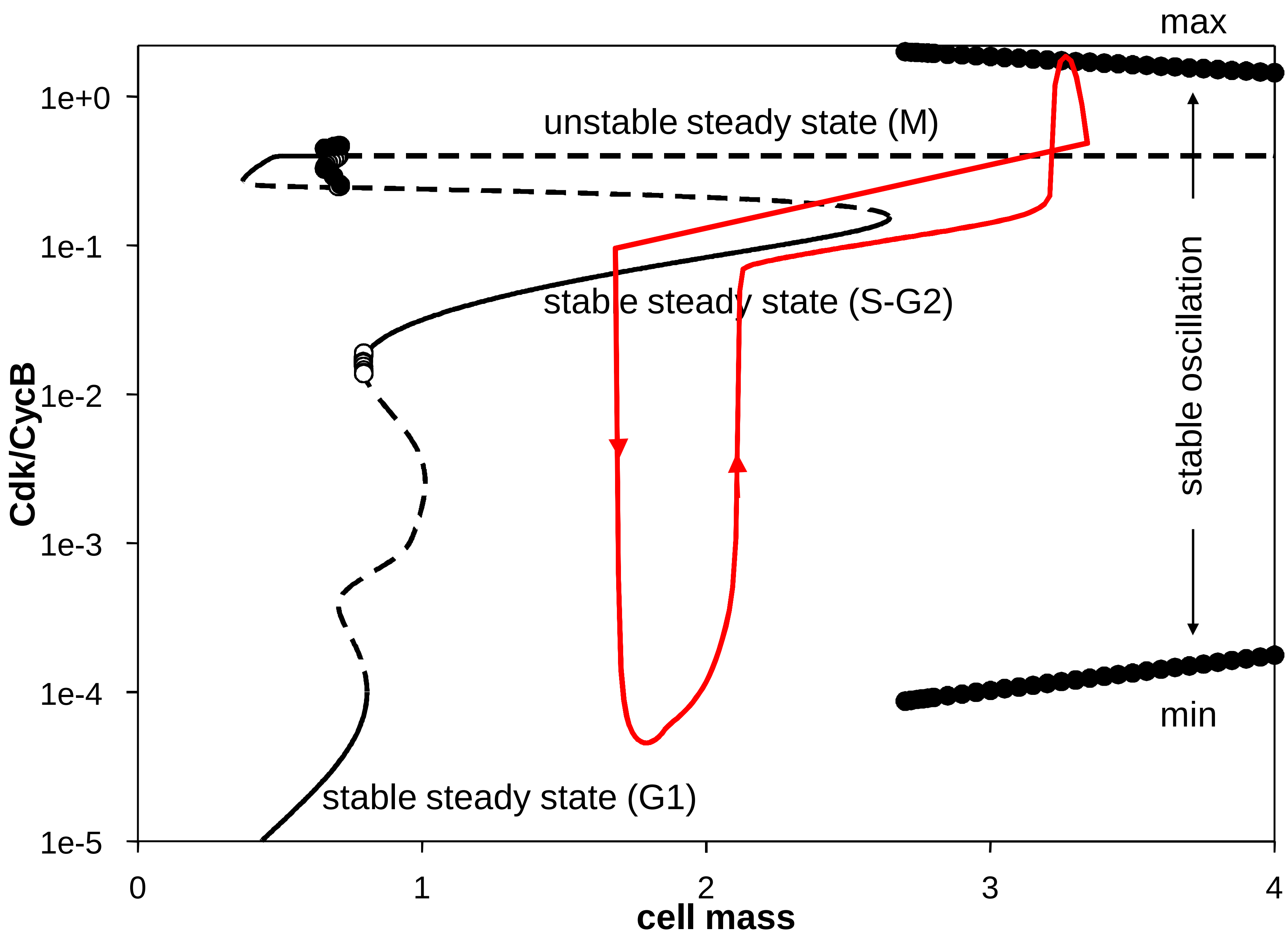


cell mass
AA
CycB
Cdk
CycB
Cdc25
CKI
Cdk
CycB
AA
G2/M
Finish
Start
Cdk/CycB
M
S/G2
10^0
10^{-1}
10^{-2}
0.1
2.0
cell mass
Cdk/CycB
M
1
1
0.1
2.0
cell mass
Cdk/CycB
M
G1
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^{-5}
0.025
0.600
cell mass

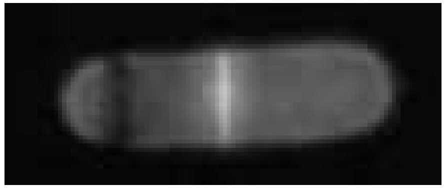


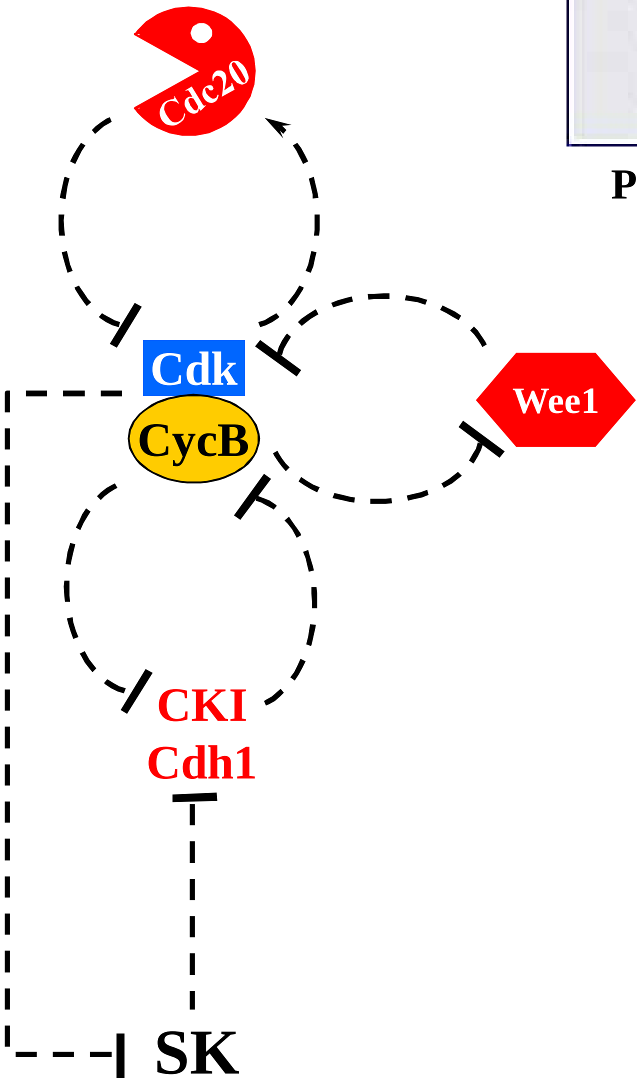
mass / nuclei
M
G1
S/G2
Cdk
CycB
time (min)
stable s.s.
unstable s.s.
min/max
M
S/G2
G1
Cdk/CycB
cell mass

Fission yeast – wild type



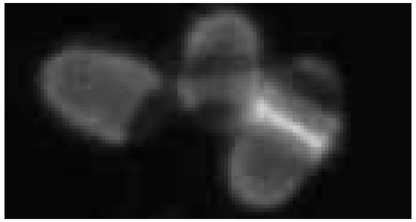
Wild type

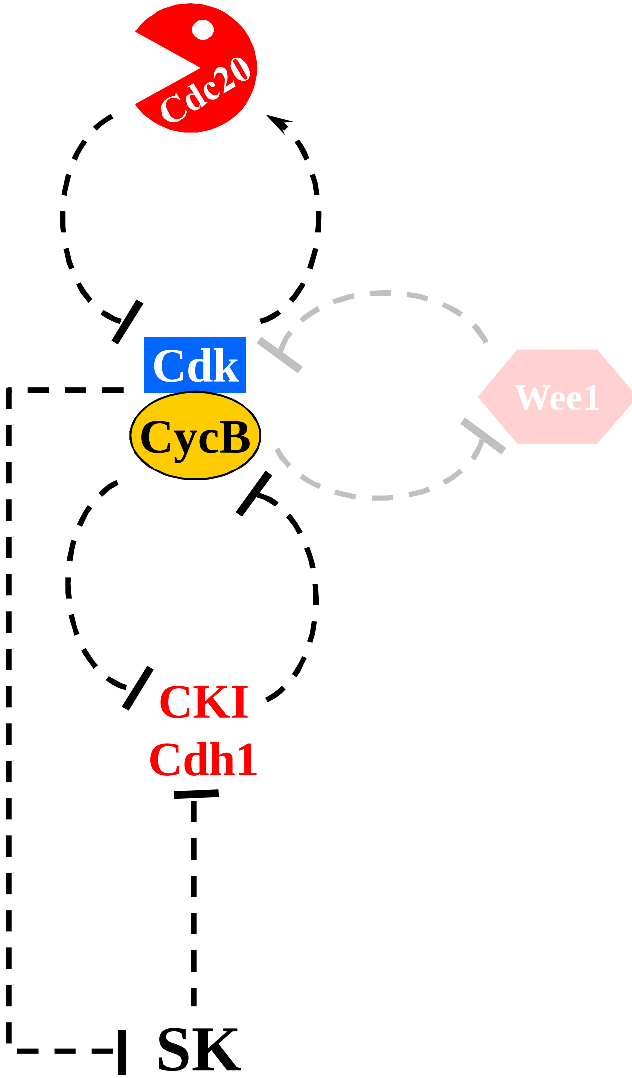


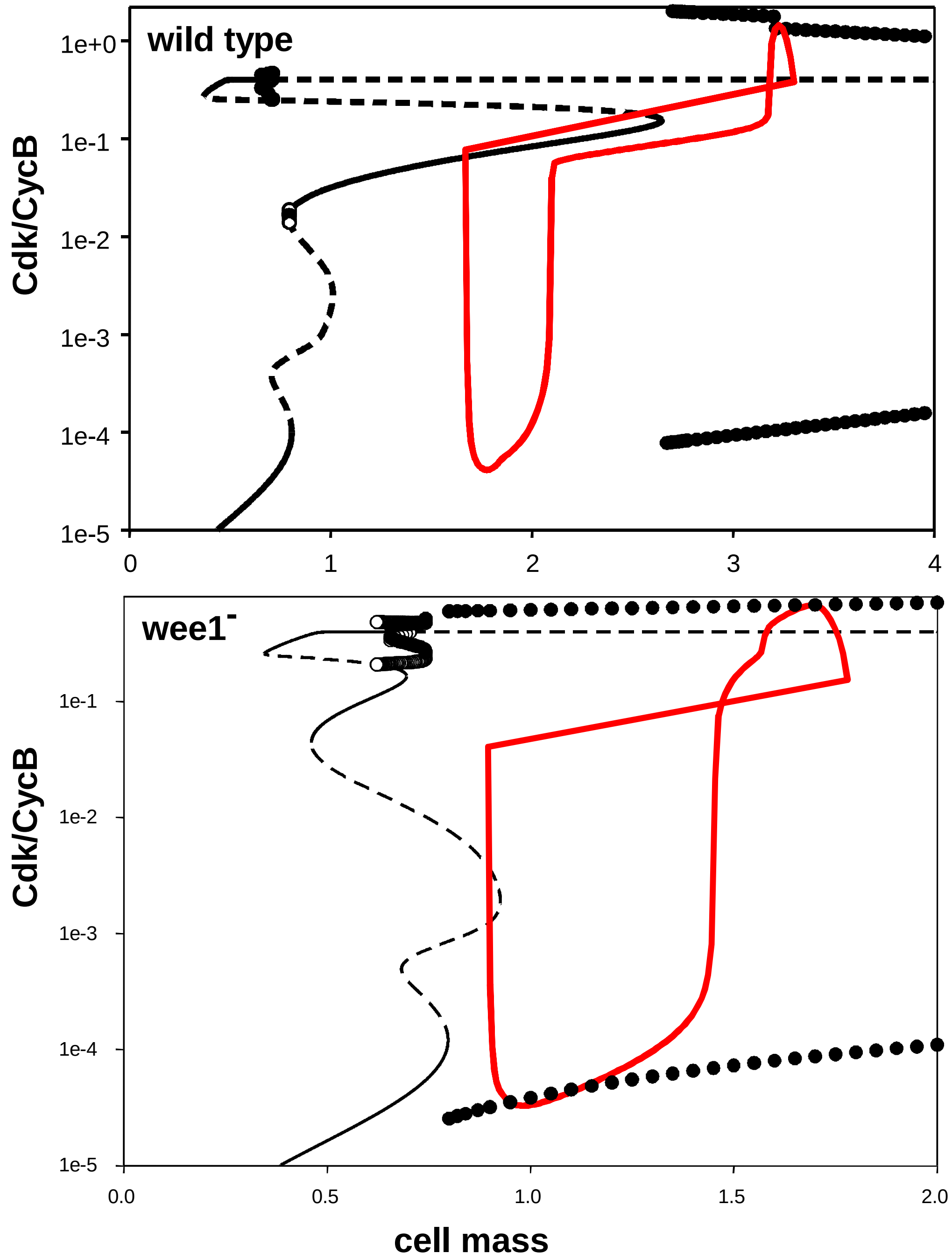


Paul Nurse

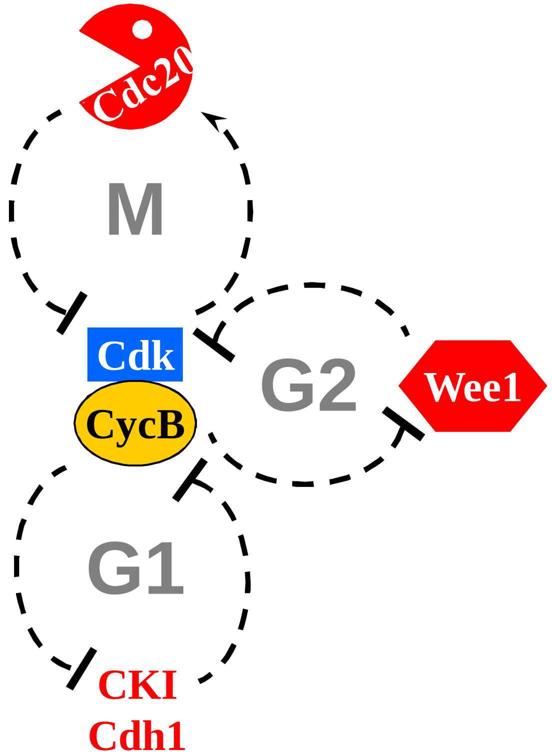
wee1^{-} **mutant**





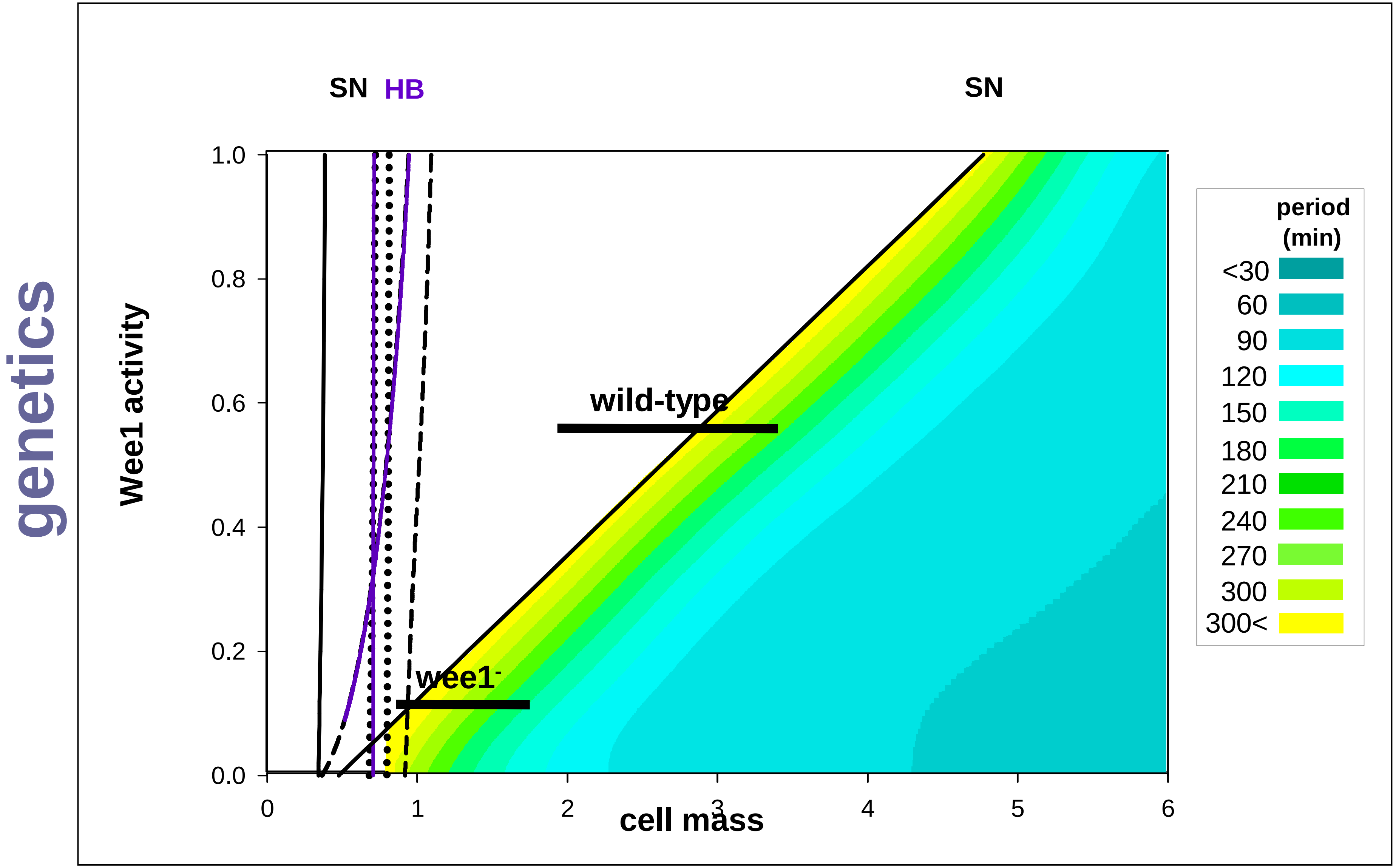


wild type
1e+0
1e-1
1e-2
1e-3
1e-4
1e-5
0
1
2
3
4
Cdk/CycB
wee1-
1e-1
1e-2
1e-3
1e-4
1e-5
0.0
0.5
1.0
1.5
2.0
Cdk/CycB
cell mass

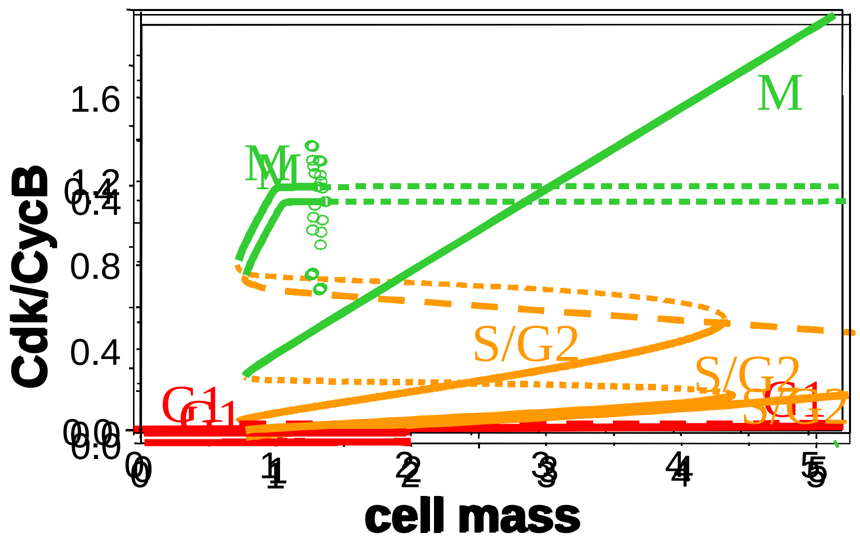


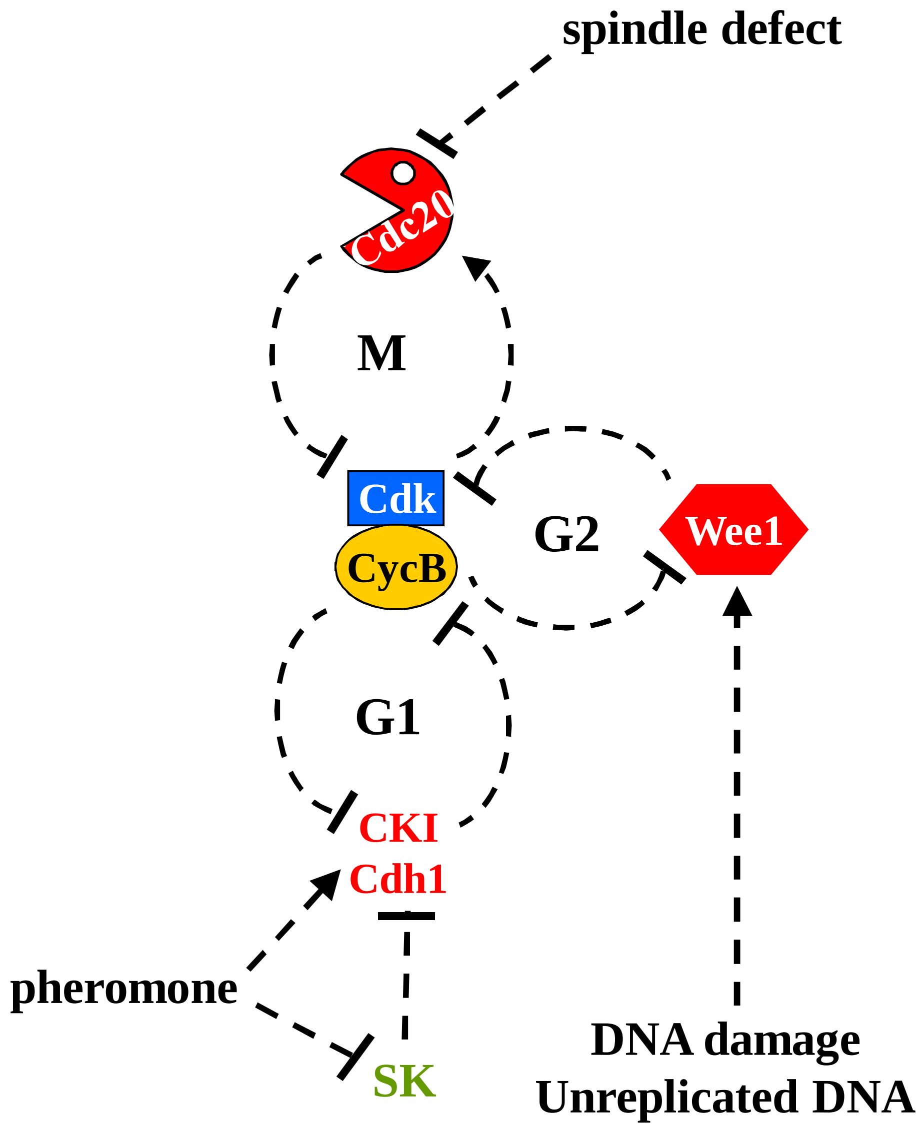
Cdc20
M
Cdk
CycB
G2
Wee1
G1
CKI
Cdh1

Two dimensional bifurcation diagram



cell physiology





BioEssays 24:1095–1109, © 2002

The dynamics of cell cycle regulation

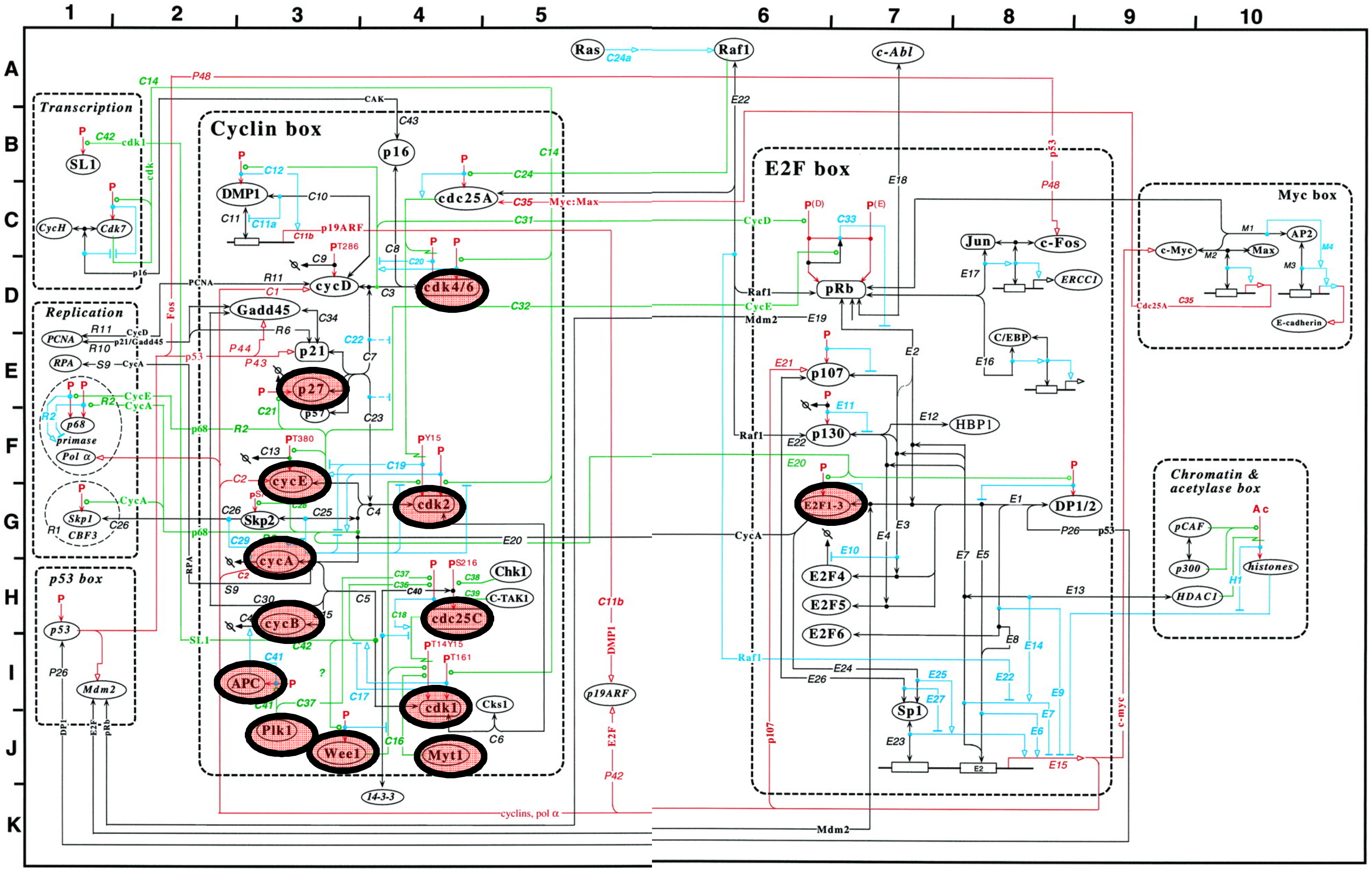
John J. Tyson,[1]* Attila Csikasz-Nagy,[2,3] and Bela Novak[2]

Molecular Biology of the Cell
Vol. 10, 2703–2734, August 1999

Molecular Interaction Map of the Mammalian Cell Cycle Control and DNA Repair Systems

Kurt W. Kohn*

Yeast homologues in our models

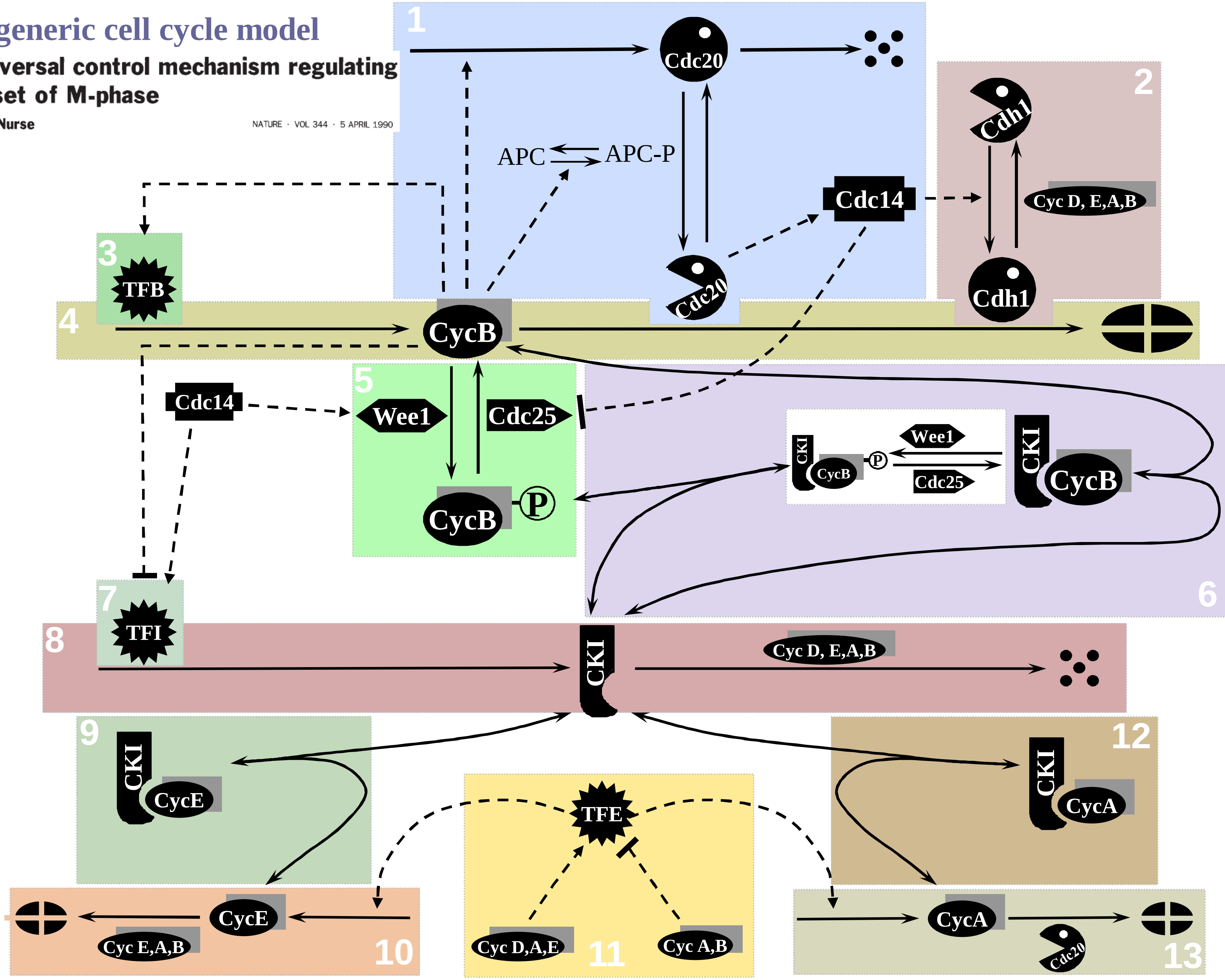


generic cell cycle model

Universal control mechanism regulating onset of M-phase

Paul Nurse

NATURE · VOL 344 · 5 APRIL 1990



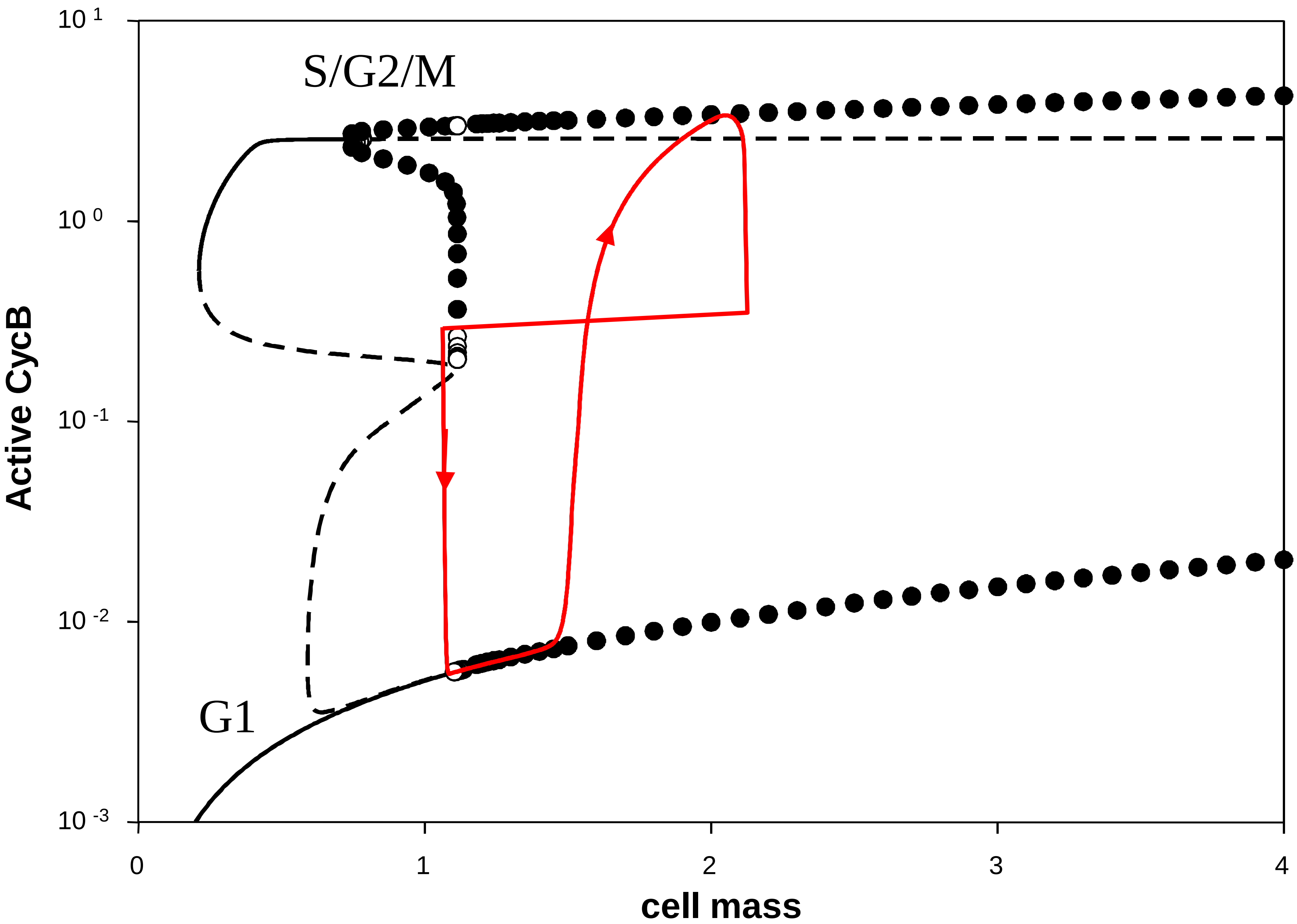
This model	Budding yeast	Fission yeast	Mammalian cells
CycB	Clb2	Cdc13	CycB
CycA	Clb5	Cig2	CycA
CycE	Cln2	-	CycE
CycD	Cln3	Puc1	CycD
CKI	Sic1	Rum1	Kip1
Cdh1	Cdh1	Ste9	Cdh1
Wee1	Swe1	Wee1	Wee1
Cdc25	Mih1	Cdc25	Cdc25c
Cdc20	Cdc20	Slp1	Cdc20
Cdc14	Cdc14	Clp1/Flp1	Cdc14
TFB	Mcm1	-	Mcm
TFE	Swi4/Swi6	Cdc10	E2F
TFI	Swi5	-	-
IE	APC	APC	APC

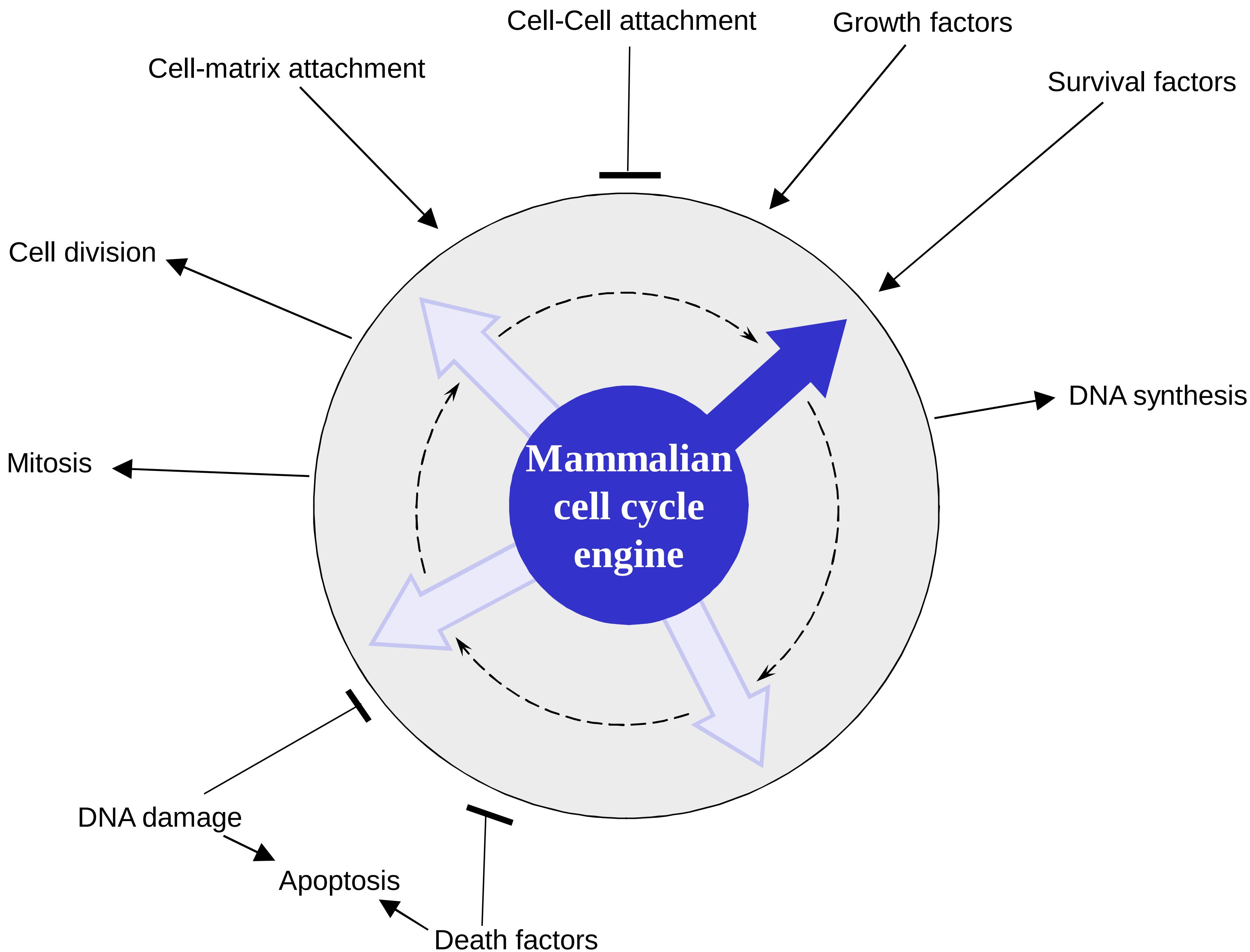
Biophysical Journal Volume 90 June 2006 4361–4379

Analysis of a Generic Model of Eukaryotic Cell-Cycle Regulation

Attila Csikász-Nagy,*† Dorjsuren Battogtokh,* Katherine C. Chen,* Béla Novák,† and John J. Tyson*

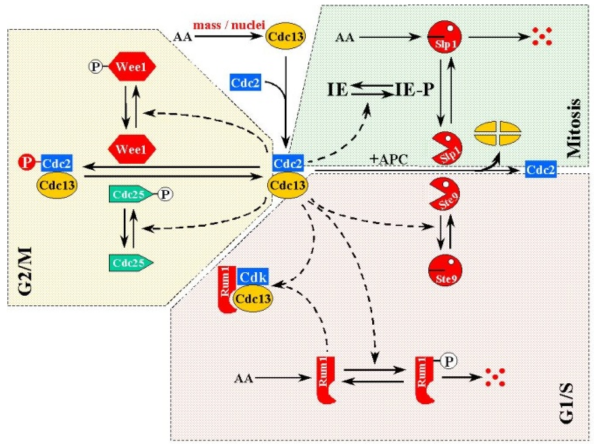
Mammalian cells




Cell-Cell attachment
Growth factors
Cell-matrix attachment
Survival factors
Cell division
DNA synthesis
Mitosis
Mammalian cell cycle engine
DNA damage
Apoptosis
Death factors

The Dynamical Perspective

Molecular Mechanism



↓

?

↓

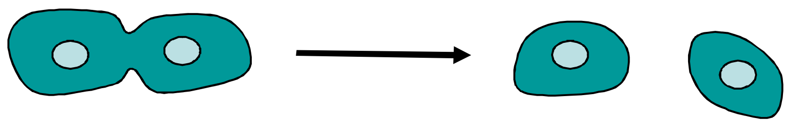
?

↓

?

↓

Physiological Properties



The Dynamical Perspective

Molecular Mechanism

↓

Kinetic Equations

↓

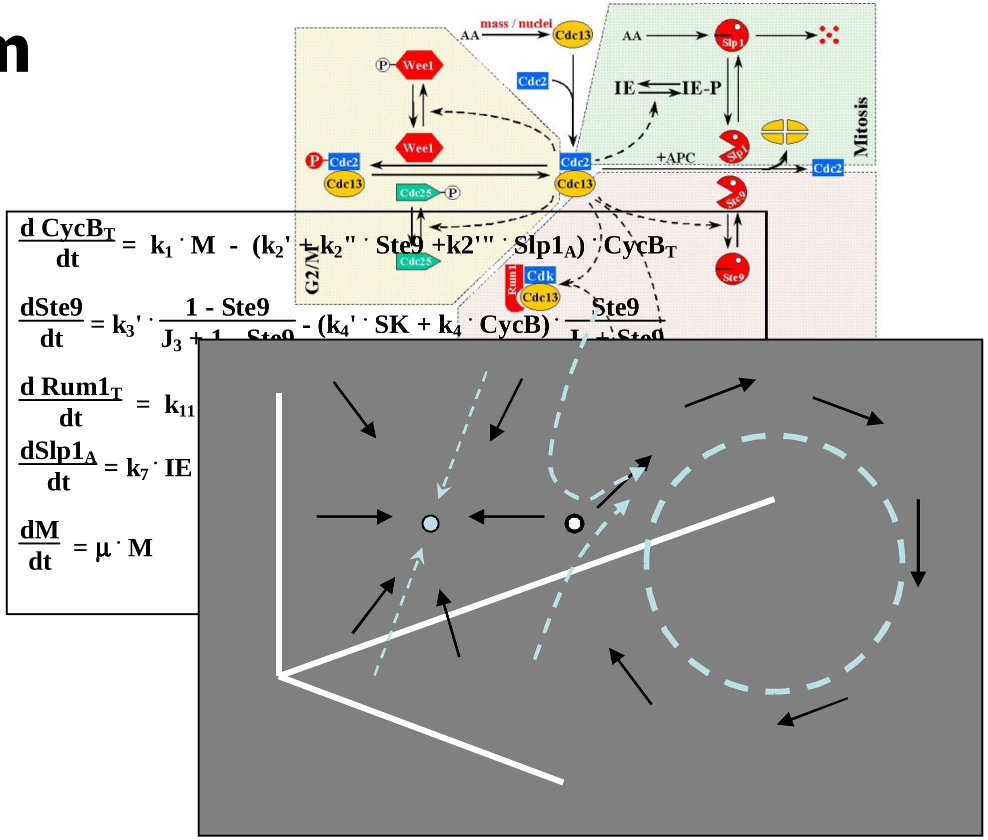
Vector Field

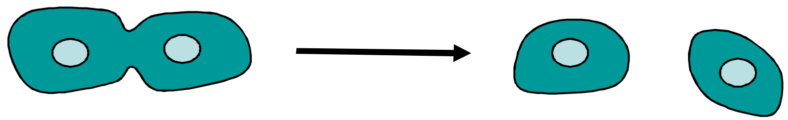
↓

Stable Attractors

↓

Physiological Properties





References:

NATURE REVIEWS | MOLECULAR CELL BIOLOGY DECEMBER 2001

NETWORK DYNAMICS AND CELL PHYSIOLOGY

John J. Tyson, Kathy Chen* and Bela Novak‡*

BioEssays 24:1095–1109, © 2002

The dynamics of cell cycle regulation

John J. Tyson,[1]* Attila Csikasz-Nagy,[2,3] and Bela Novak[2]

Reverse Engineering Models of Cell Cycle Regulation

Attila Csikász-Nagy,* Béla Novák and John J. Tyson

Adv Exp Med Biol. 2008;641:88-97.

BRIEFINGS IN BIOINFORMATICS. page 1 of 11 doi:10.1093/bib/bbp005

Computational systems biology of the cell cycle

Attila Csikász-Nagy

Acknowledgements:

The Microsoft Research - University of Trento
Centre for Computational and Systems Biology

Budapest University of Technology and Economics

VirginiaTech
1872
VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY

UNIVERSITY OF OXFORD

IFOM
ISTITUTO FIRC DI ONCOLOGIA MOLECOLARE

John J. Tyson

Béla Novak

Kathy Chen

Andrea Ciliberto

Ákos Sveiczer