A Generic Model of Cell Cycle Regulation in Eukaryotes

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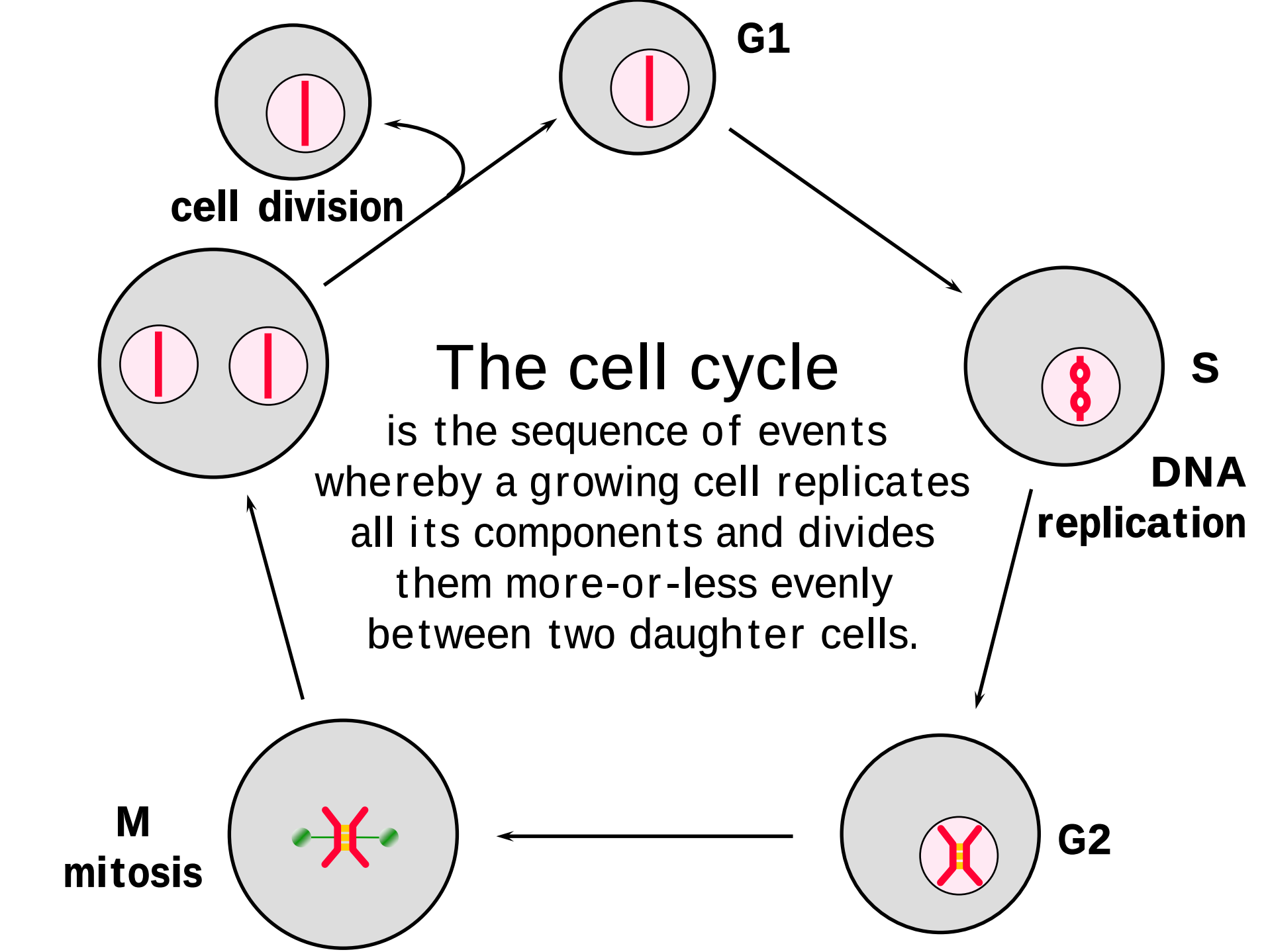
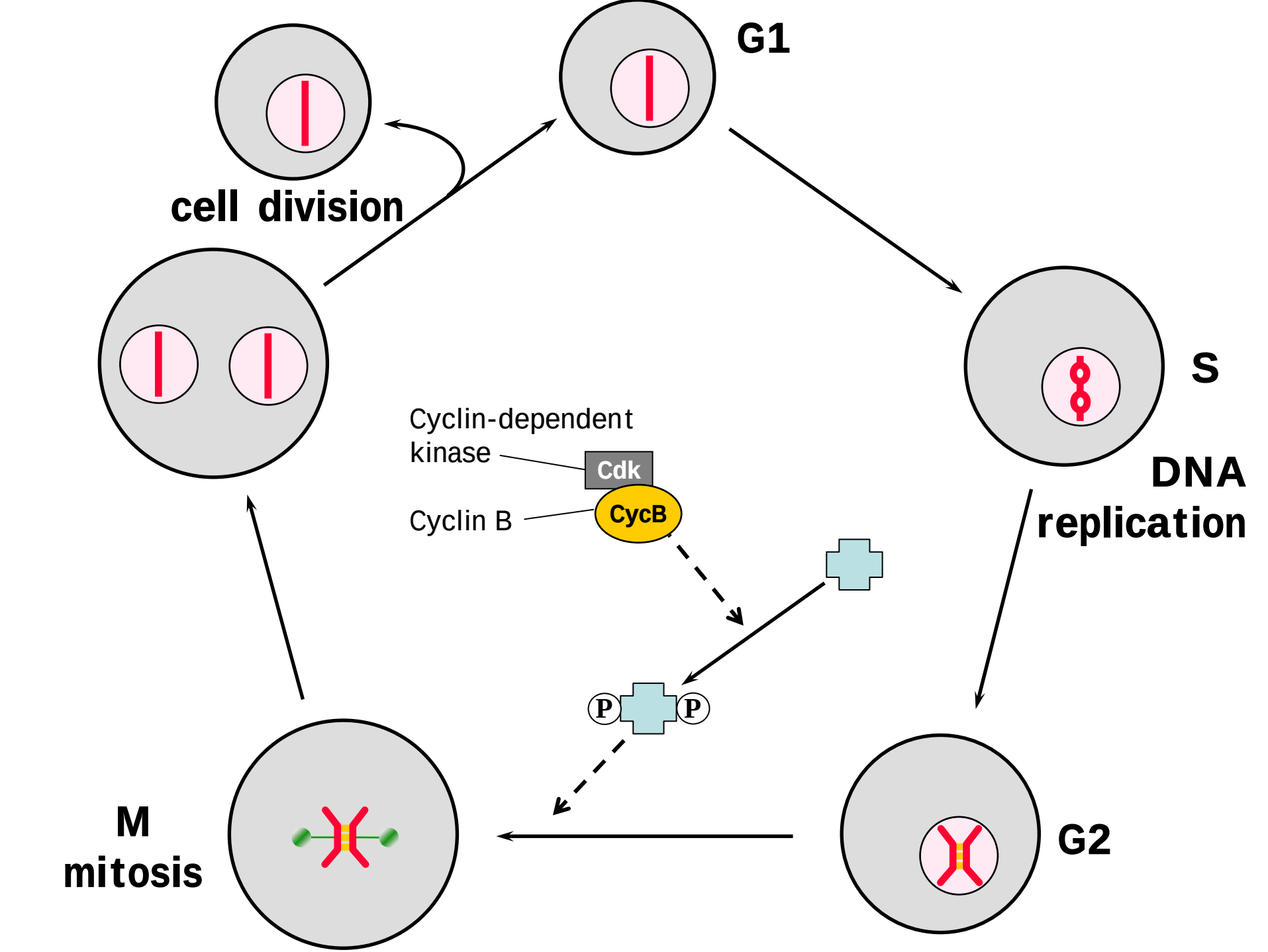
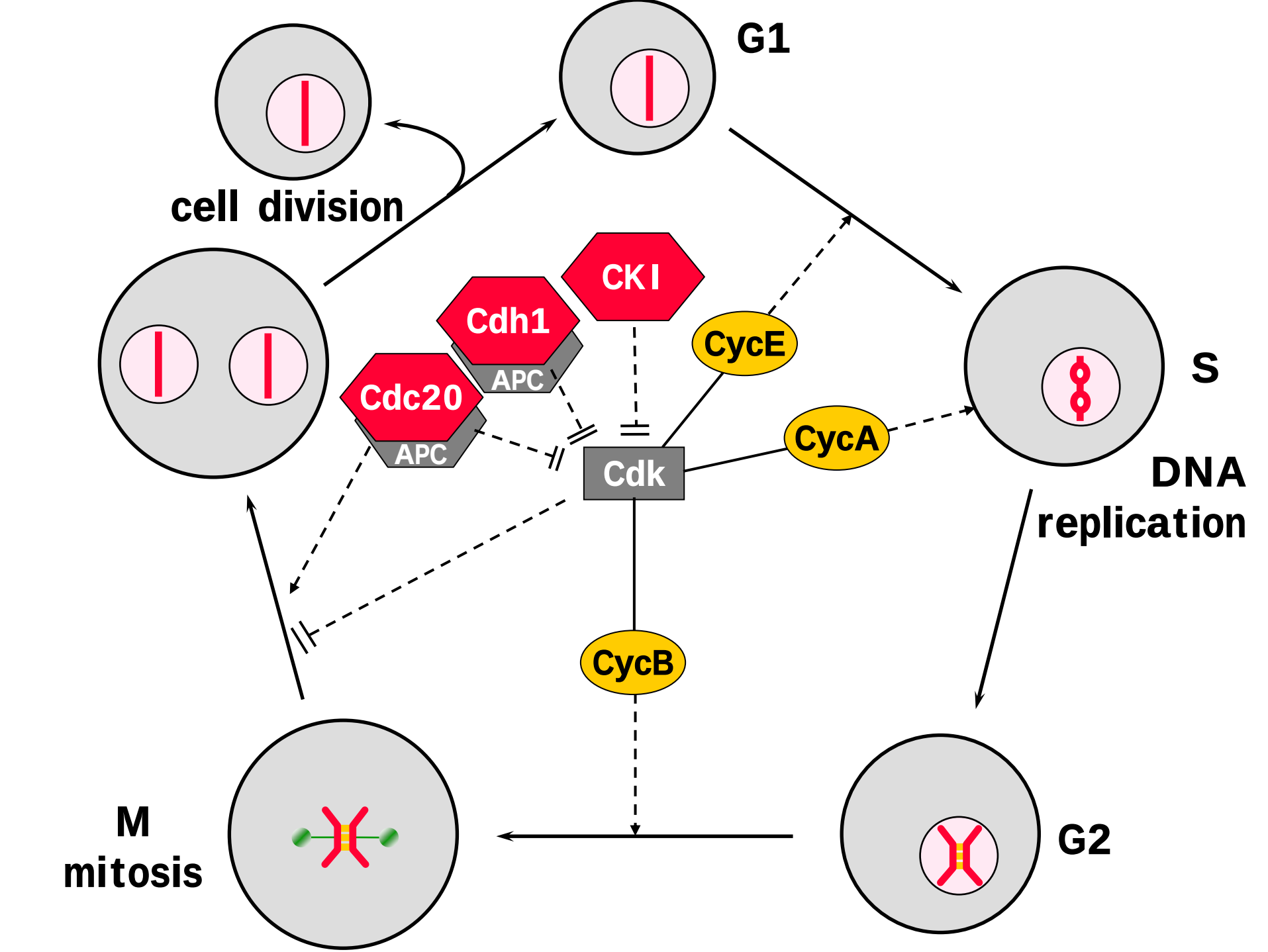
- James S. McDonnell Foundation

Cyclic & Dynamic Behaviors

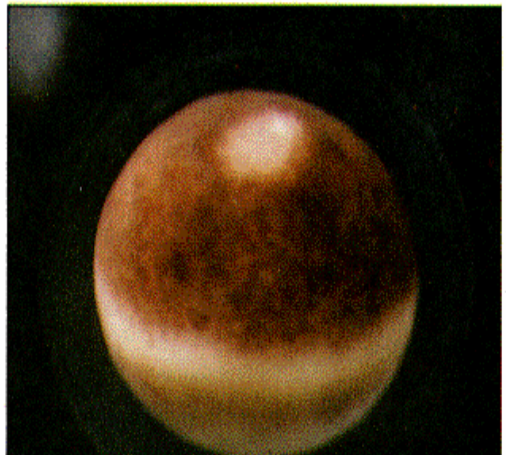
Neural oscillations	0.01-1 sec
Calcium oscillations	1-100 sec
Hormonal rhythms	min - hours
Cell cycle	hours - days
Circadian rhythms	1 day


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.

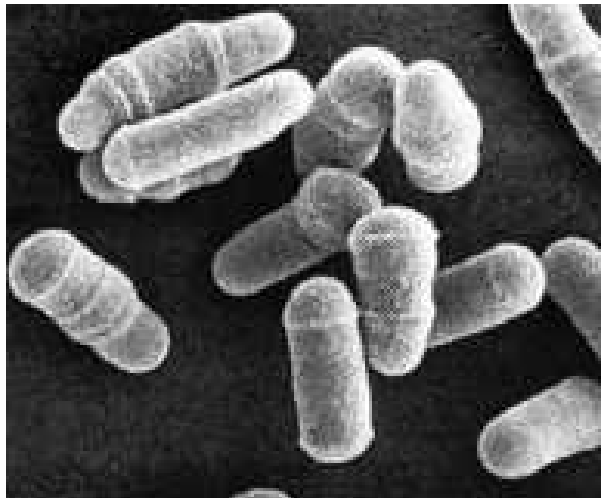

G1
cell division
S
DNA
replication
Cyclin-dependent
kinase
Cdk
Cyclin B
CycB
P
P
M
mitosis
G2


G1
cell division
CKI
Cdh1
APC
Cdc20
APC
CycE
CycA
Cdk
S
DNA
replication
CycB
M
mitosis
G2

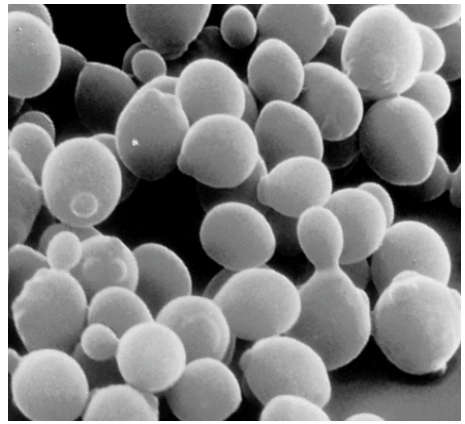
Frog Egg



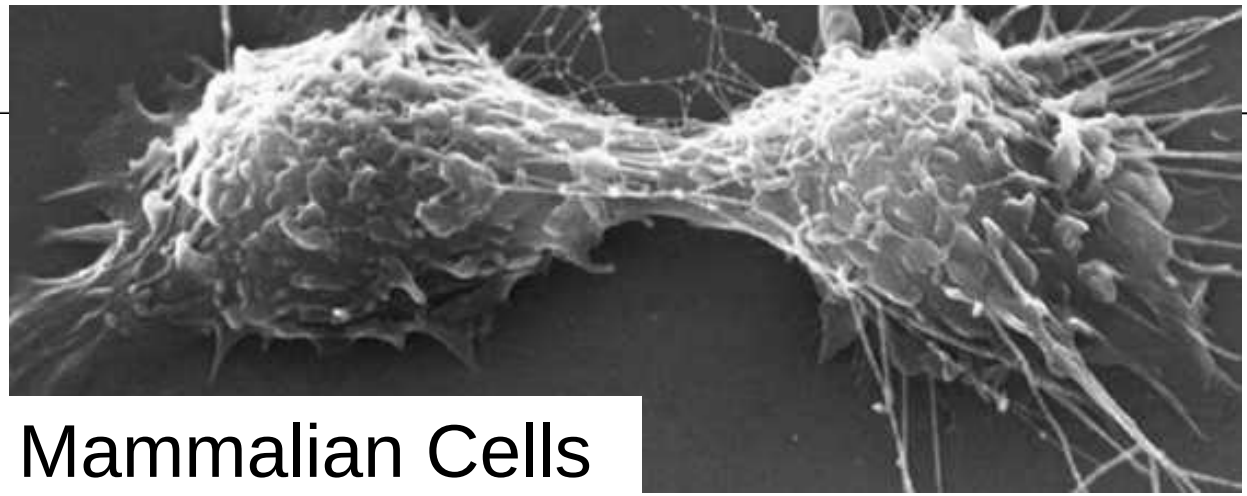
Fission Yeast



Budding Yeast



Is the control mechanism universal?



Mammalian Cells

Gene conversion table

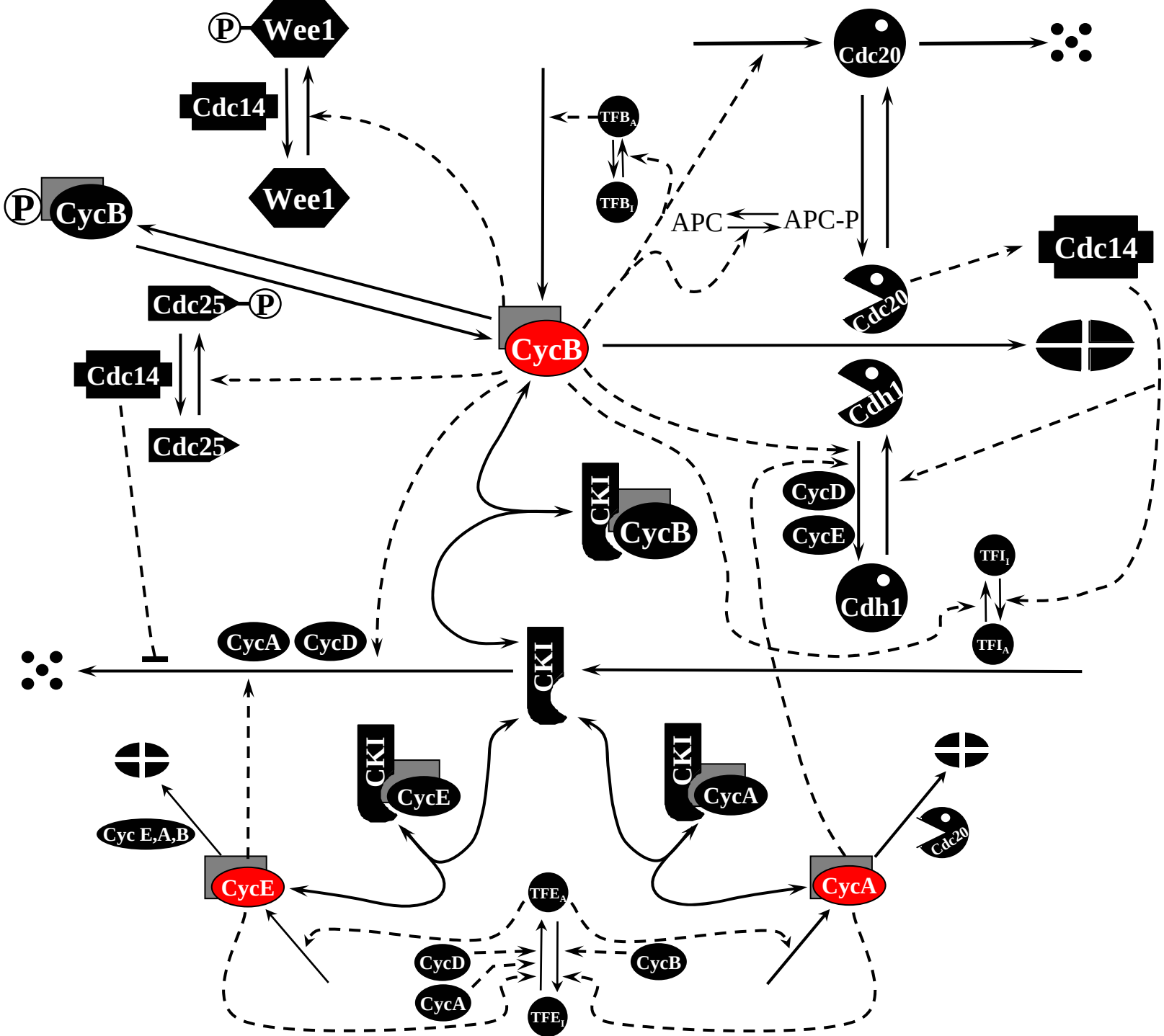
Frog egg	Budding Y	Fission Y	Mammalian
Cdc2	Cdc2	Cdc28	Cdk1, Cdk2
CycB	Clb2	Cdc13	CycB
CycA	Clb5	Cig2	CycA
CycE	Cln2	-	CycE

Is the control mechanism governed by the same dynamical principles in all eukaryotes?

Fizzy	Cdc20	Slp1	Cdc20
?	Cdc14	Clp1/Flp1	Cdc14
Mcm	Mcm1	-	Mcm
E2F	Swi4/Swi6	Cdc10	E2F
-	Swi5	-	-
APC	APC	APC	APC

Thesis 1.

The wiring diagram is (essentially) universal; the parameter values vary from organism to organism.


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$_A$
CKI
CycB
CycA
CycD
CKI
CKI
CycE
CKI
CycA
Cyc E,A,B
CycE
CycA
Cdc20
TFE$_A$
CycD
CycA
CycB
TFE$_I$

18 algebraic equations

Cdc14=Cdc20A

Vdb=kdbp+kdbpp*Cdh1+kdbppp*Cdc20A

TFB=GK(kafb*actMPF,kifb,Jafb,Jifb)

Wee1=GK(kaweep+kaweepp*Cdc14,kiwee*actMPF,Jawee,Jiwee)

Vwee=kweep+kweepp*Wee1

Cdc25=(GK(ka25*actMPF,ki25p+ki25pp*Cdc14,Ja25,Ji25))

V25=k25p+k25pp*Cdc25

Vdi=(kdip+kdipp*actCycA+kdippp*actMPF+kdipppp*actCycE+kdippppp*SK*m)/(1.0+k14di*Cdc14)

TriA=CycA-actCycA

TriE=CycE-actCycE

freeCKI=CKI-TriB-TriA-TriE

Vde=(kdep+kdepp*actCycE+kdeppp*actCycA+kdepppp*actMPF)

TFI=GK(kafi*Cdc14,kifip+kifipp*actMPF,Jafi,Jifi)

Vsi=ksip+ksipp*TFI

Vsb=ksbp+ksbpp*TFB

Vda=kdap+kdapp*Cdc20A+kdappp*Cdc20T

Vatf=katfp+katfpp*actCycA+katfppp*actCycE+katfpppp*SK*m

TFE=GK(Vatf,kitfp+kitfpp*actMPF+kitfppp*actCycA,Jatf,Jitf)

13 differential equations

dactCycA/dt=((ksap+ksapp*TFE)*m+Vdi*TriA+kdia*TriA) - ((Vda+kasa*freeCKI)*actCycA)

dactMPF/dt=(Vsb*m+V25*(CycB-TriB-actMPF)+(kdib+Vdi)*(CycB-preMPF-actMPF)) - ((Vdb+Vwee+kasb*freeCKI)*actMPF)

dCdc20A/dt=(ka20*IEP*(Cdc20T-Cdc20A)/(Ja20+Cdc20T-Cdc20A)) - ((ki20/(Ji20+Cdc20A)+kd20)*Cdc20A)

dCdc20T/dt=(ks20p+ks20pp*actMPF^n20/(J20^n20+actMPF^n20)) - (kd20*Cdc20T)

dCdh1/dt=((kah1p+kah1pp*Cdc14)*(1.0-Cdh1)/(Jah1+1.0-Cdh1)) -
(((kih1p+kih1pp*actCycA+kih1ppp*actMPF+kih1pppp*actCycE+kih1ppppp*SK*m)/(Jih1+Cdh1))*Cdh1)

dCKI/dt=(Vsi) - (Vdi*CKI)

dCycE/dt=((ksep+ksepp*TFE)*m) - (Vde*CycE)

dactCycE/dt= ((ksep+ksepp*TFE)*m) + ((kdie+Vdi)*(CycE-actCycE)) - ((kase*freeCKI+Vde)*actCycE)

dCycB/dt=(Vsb*m) - (Vdb*CycB)

dCycA/dt=((ksap+ksapp*TFE)*m) - (Vda*CycA)

dIEP/dt=(kaie*actMPF*(1.0-IEP)/(Jaie+1.0-IEP)) - ((kiie/(Jiie+IEP))*IEP)

dpreMPF/dt=(Vwee*(CycB-preMPF)) - ((V25+Vdb)*preMPF)

dTriB/dt=(kasb*(CycB-TriB)*freeCKI) - ((kdib+Vdb+Vdi)*TriB)

86 parameters

kasb
kase
katfp
katfpp
katfppp
katfpppp
kaweep
kaweepp
kd20
kdap
kdapp
kdappp
kdbp
kdbpp
kdbppp
kdep

etc.

Parameter Tables

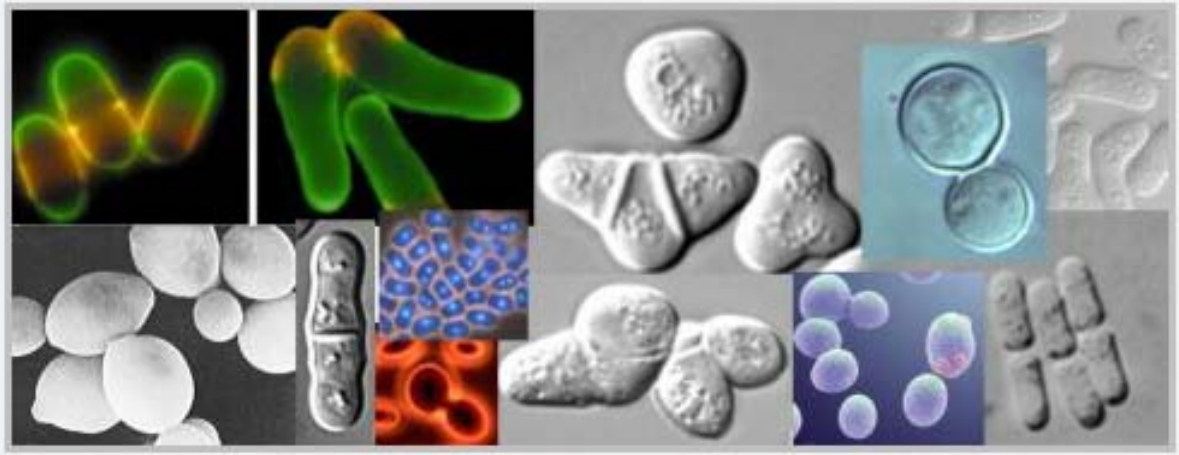
	BUDDING	MAMMALIAN	POMBE	MORPHO	FROG
J20	100	100	0.05	100	0
Ja20	10	0.005	0.001	10	0.1
Ja25	0	0	0.01	0.1	0.1
Jafb	0.1	0.1	0	0.1	0
Jafi	10	0	0	10	0
Jah1	0.03	0.01	0.01	0.03	0
Jaie	0.1	0.01	0.001	0.1	0.01
Jatf	0.01	0.01	0.01	0.01	0
Jawee	0	0	0.01	0.05	0.3
Ji20	10	0.005	0.001	10	0.1
Ji25	0	0	0.01	0.1	0.1
Jifb	0.1	0.1	0	0.1	0
Jifi	10	0	0	10	0
Jih1	0.03	0.01	0.01	0.03	0
Jiie	0.1	0.01	0.001	0.1	0.01
Jitf	0.01	0.01	0.01	0.01	0
Jiwee	0	0	0.01	0.05	0.3
k14di	12	0	0	12	0
k25p	0	0	0.001	0.05	0.1
k25pp	0	0	1	0.5	1.9
ka20	1	0.5	0.2	1	0.1
ka25	0	0	1	1	1
kafb	1	1	0	1	0
kafi	6	0	0	6	0
kah1p	0.01	0.75	5	0.01	0
kah1pp	0.8	14	50	0.8	0
kaie	0.1	0.07	0.2	0.1	2
kasa	50	100	500	50	0

	BUDDING	MAMMALIAN	POMBE	MORPHO	FROG
kasb	65	0	1000	65	0
kase	0	100	0	0	0
katfp	0	0	1.5	0	0
katfpp	0.76	0.3	0	0.76	0
katfppp	0.76	0.5	0	0.76	0
katfpppp	3.8	0.33	0	3.8	0
kaweep	0	0	0.25	0.3	0.1
kaweepp	0	0	0.25	0	0
kd20	0.05	0.15	0.1	0.05	1
kdap	0.01	0.002	0.01	0.01	0
kdapp	0.16	2	2	0.16	0
kdappp	0	0	0.02	0	0
kdbp	0.003	0.005	0.02	0.003	0.015
kdbpp	0.4	2	0.75	0.4	0
kdbppp	0.15	0.1	1.5	0.15	0.985
kdep	0.12	0.01	0	0.12	0
kdepp	0	0.1	0	0	0
kdeppp	0	1	0	0	0
kdepppp	0	1	0	0	0
kdia	0.06	1	1	0.06	0
kdib	0.05	0	1	0.05	0
kdie	0	1	0	0	0
kdip	0.02	1	0.1	0.02	0
kdipp	0.2	5	2	0.2	0
kdippp	0.9	10	100	0.9	0
kdipppp	0.12	5	0	0.12	0
kdippppp	0.66	0	1	0.66	0
ki20	0.05	0.25	0.05	0.05	0.095

	BUDDING	MAMMALIAN	POMBE	MORPHO	FROG
ki25p	0	0	0.25	0.3	0.125
ki25pp	0	0	0.25	0	0
kifb	0.15	0.1	0	0.15	0
kifip	0.008	0	0	0.008	0
kifipp	0.05	0	0	0.05	0
kih1p	0.001	0	1	0.001	0
kih1pp	0.64	1.2	40	0.64	0
kih1ppp	0.1	4	40	0.1	0
kih1pppp	0.032	0	0	0.032	0
kih1ppppp	0.01	0	40	0.01	0
kiie	0.15	0.18	0.08	0.15	0.15
kitfp	0.6	0.25	1	0.6	0
kitfpp	8	0.1	0	8	0
kitfppp	0	0.1	10	0	0
kiwee	0	0	1	1	3
ks20p	0.001	0	0.005	0.001	1
ks20pp	10	15	0.1	10	0
ksap	0.0008	0	0	0.0008	0
ksapp	0.005	0.025	0.02	0.005	0
ksbp	0.004	0.01	0.02	0.004	0.1
ksbpp	0.04	0.03	0	0.04	0
ksep	0	0.008	0	0	0
ksepp	0.15	0.3	0	0.15	0
ksip	0.036	2	0.3	0.036	0
ksipp	0.24	0	0	0.24	0
kweep	0	0	0.05	0.2	0.1
kweepp	0	0	0.5	2	0.9
m	0.1	0.1	0.1	0.1	0.001
n20	1	1	4	1	0
SK	0.108	0.5	0.05	0.108	0

Red rectangle: Parameter is not used in simulations of that organism

Welcome to the Generic Cell Cycle Homepage



1 2 2 0

This is the companion website to the paper:

Attila Csikasz-Nagy, Dorjsuren Battogtokh, Kathy Chen, Bela Novak & John J. Tyson

Analysis of a generic model of eukaryotic cell cycle regulation

published in Biophysical Journal (2006) 90:4361-79

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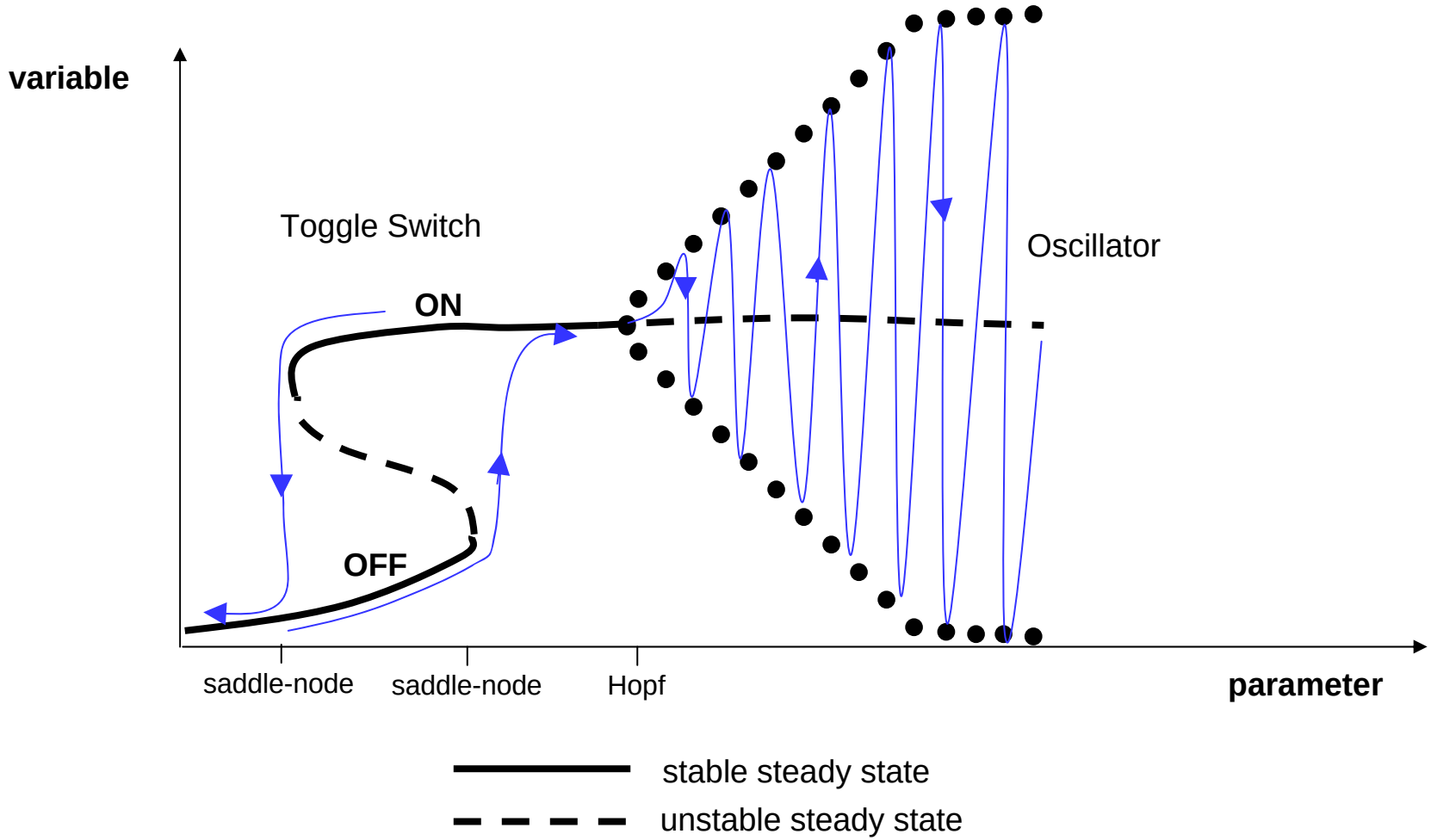
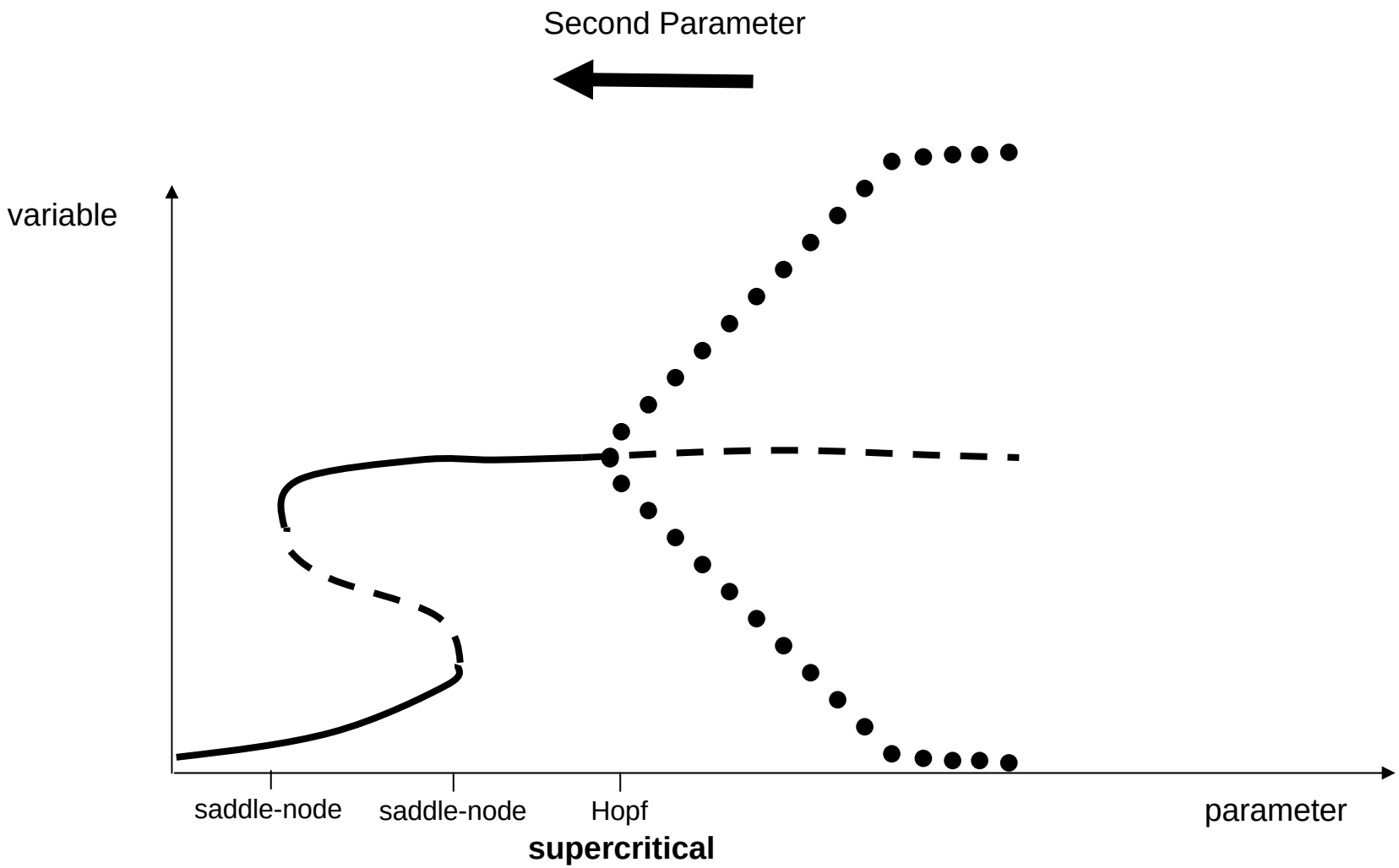
www.mpf.biol.vt.edu

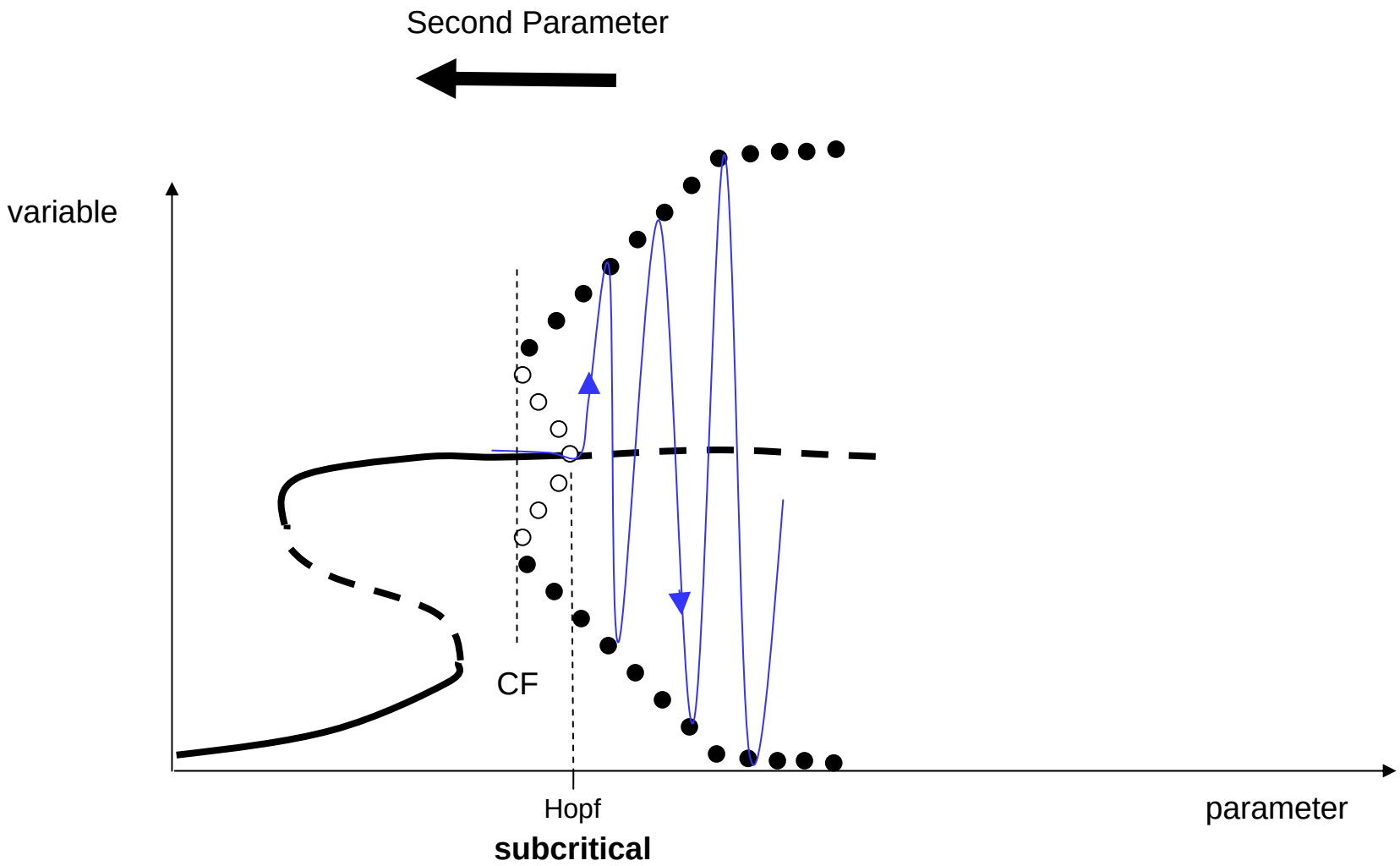
Thesis 2.

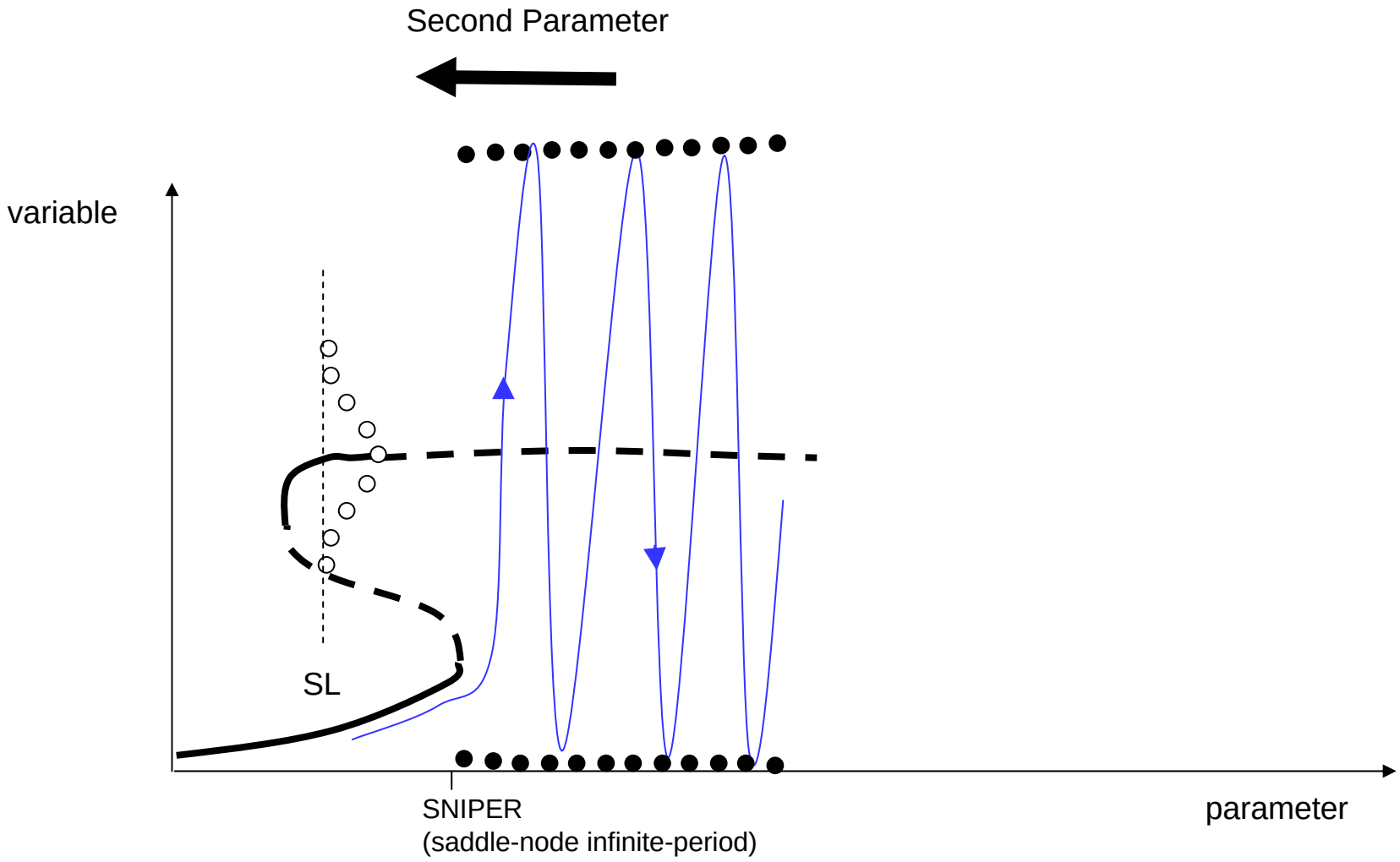
One-parameter bifurcation diagrams govern progression through the cell cycle.

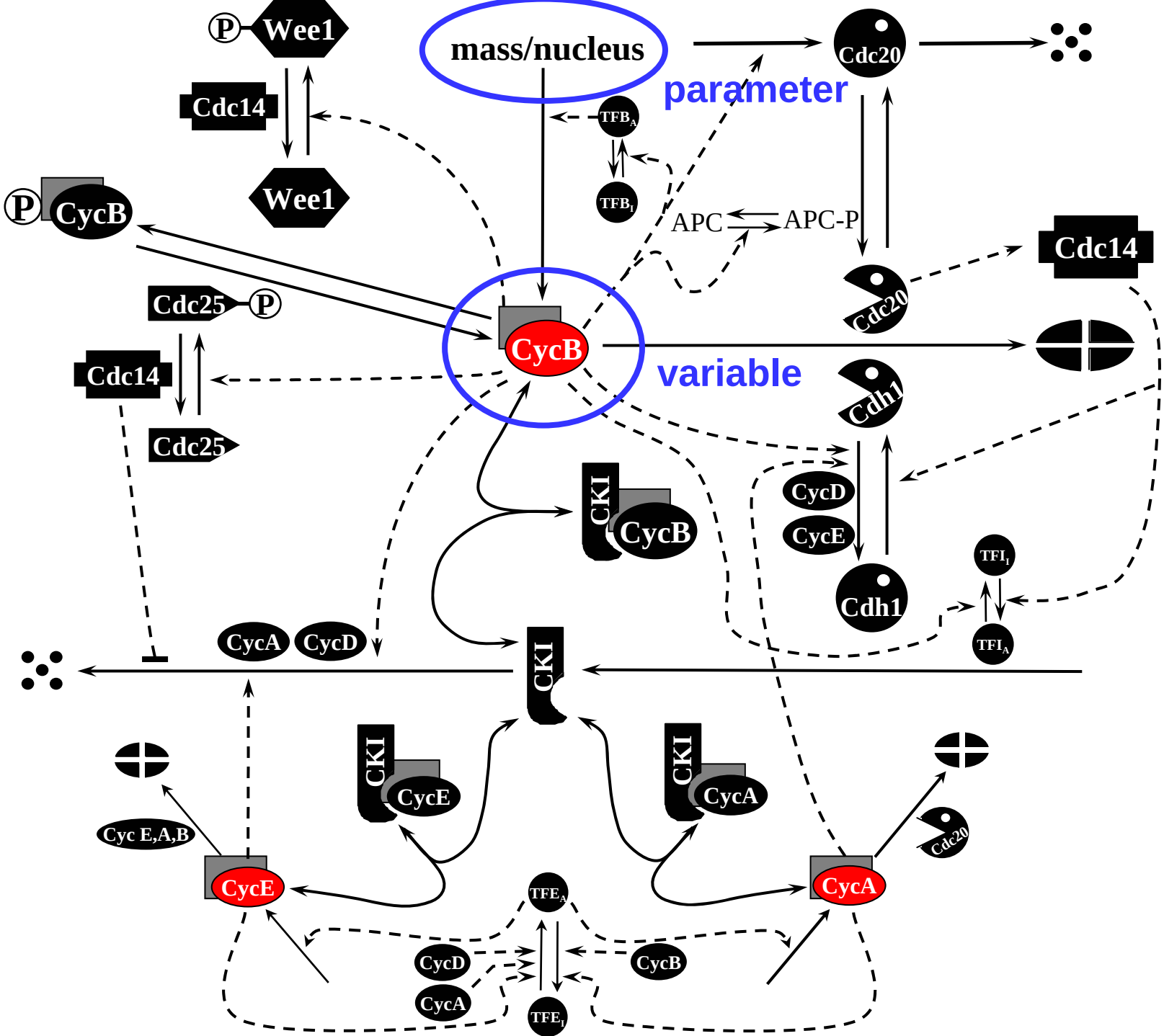
One-parameter bifurcation diagram

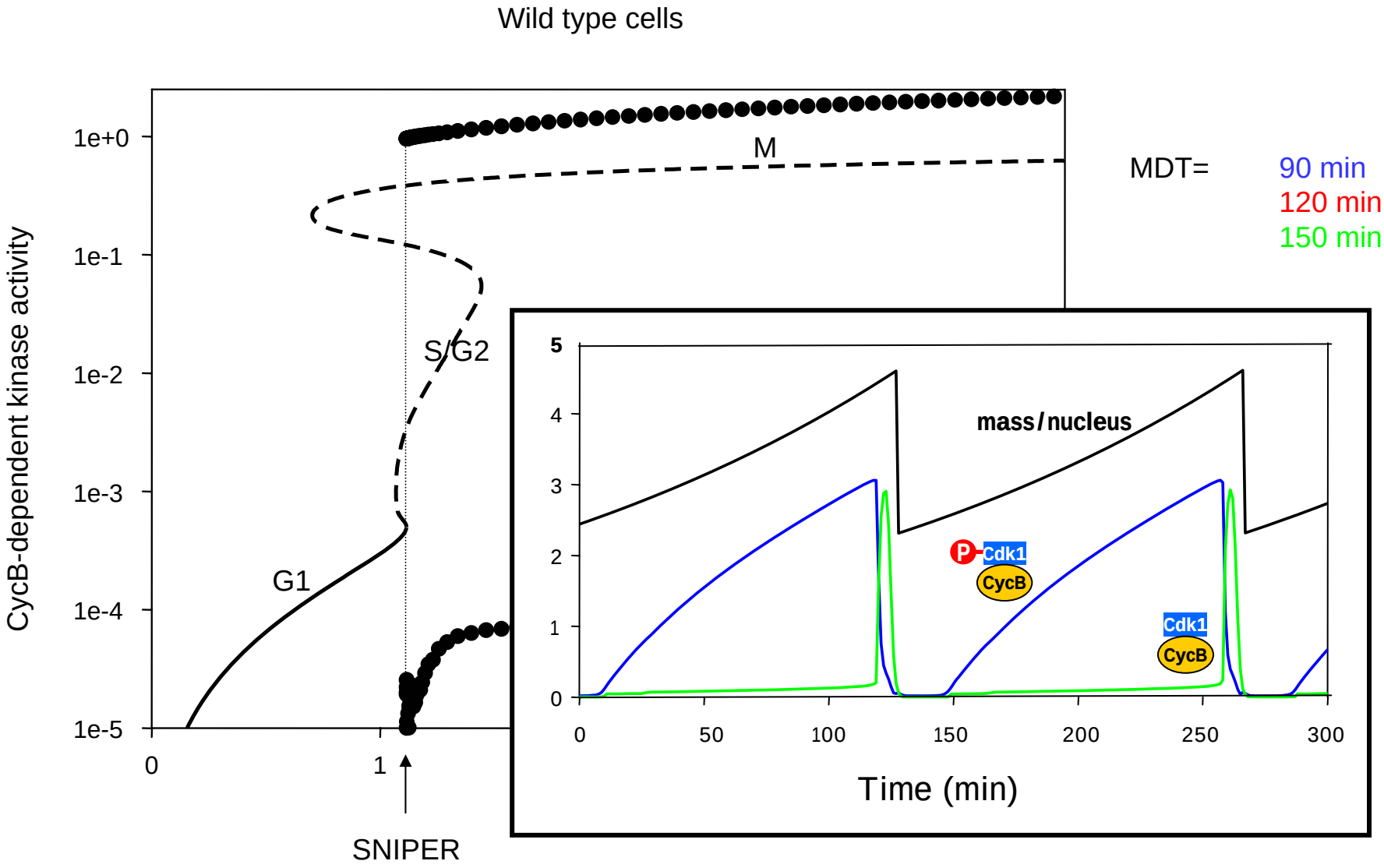


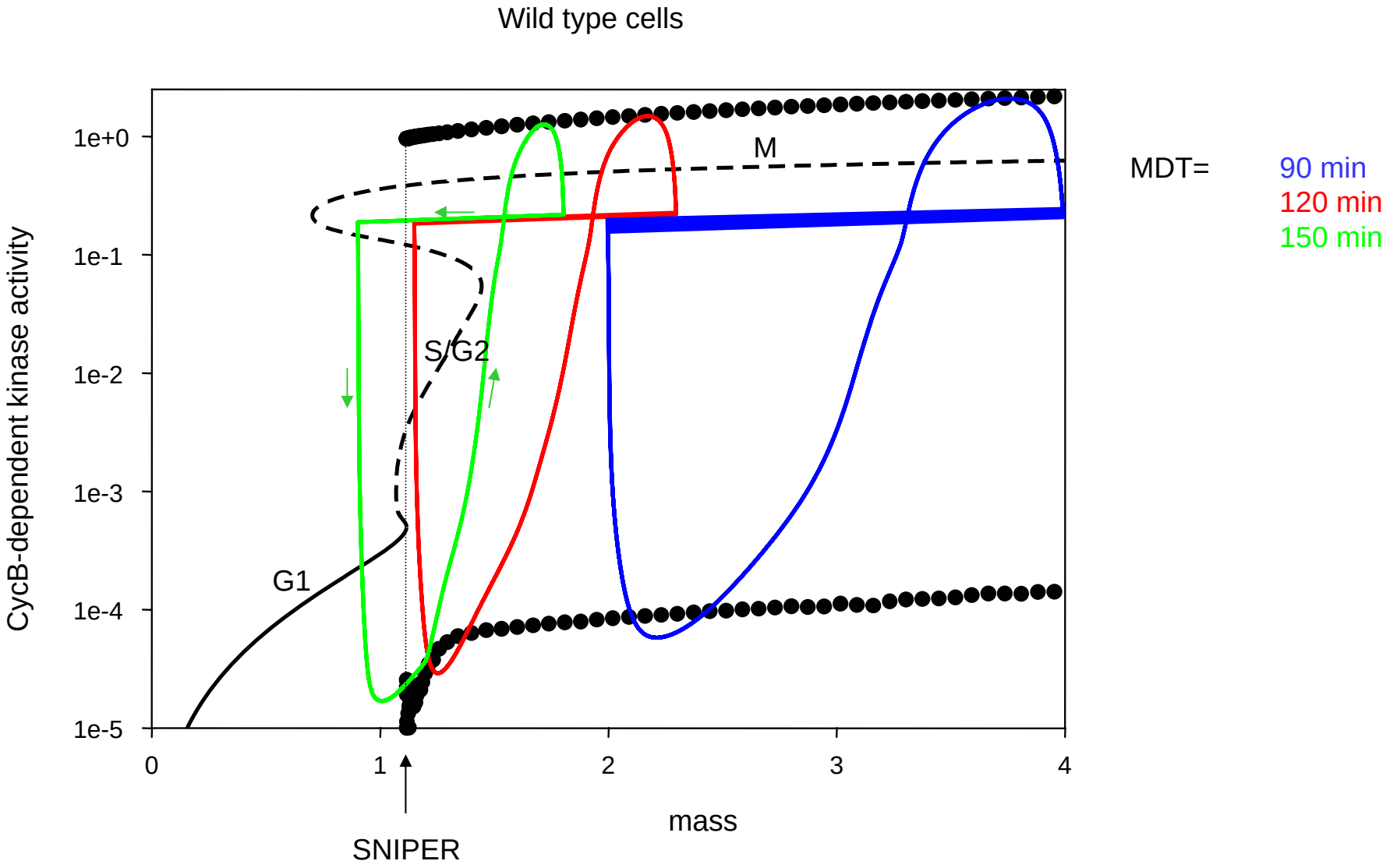

Second Parameter
variable
saddle-node
saddle-node
Hopf
parameter
supercritical

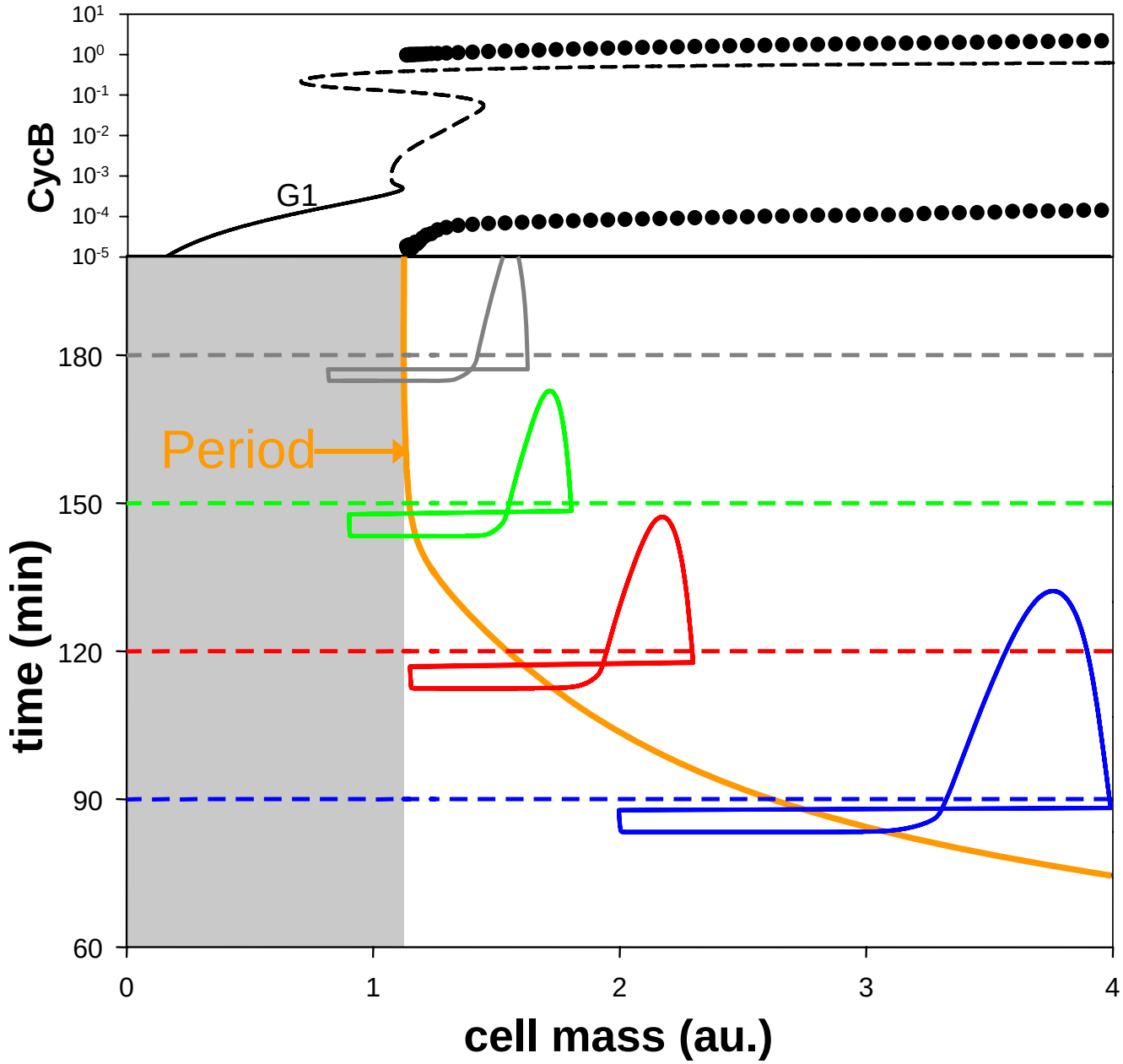

Second Parameter
variable
CF
Hopf
parameter
subcritical


Second Parameter
variable
SL
SNIPER
(saddle-node infinite-period)
parameter


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

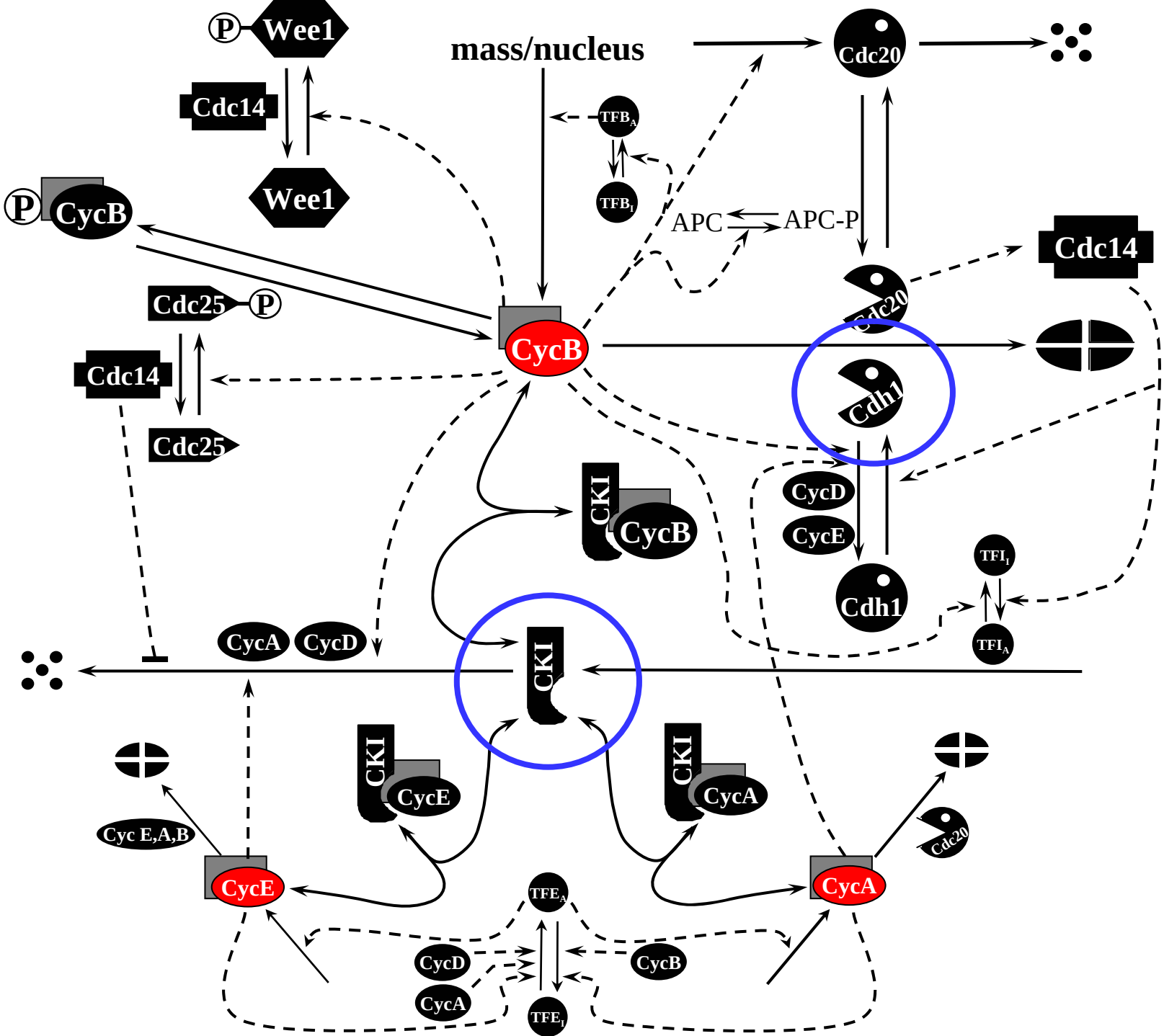

Wild type cells
CycB-dependent kinase activity
1e+0
1e-1
1e-2
1e-3
1e-4
1e-5
0
1
M
S/G2
G1
SNIPER
MDT=
90 min
120 min
150 min
5
4
3
2
1
0
mass/nucleus
P
Cdk1
CycB
Cdk1
CycB
0
50
100
150
200
250
300
Time (min)


Wild type cells
CycB-dependent kinase activity
1e+0
1e-1
1e-2
1e-3
1e-4
1e-5
0
1
2
3
4
mass
M
S/G2
G1
SNIPER
MDT=
90 min
120 min
150 min

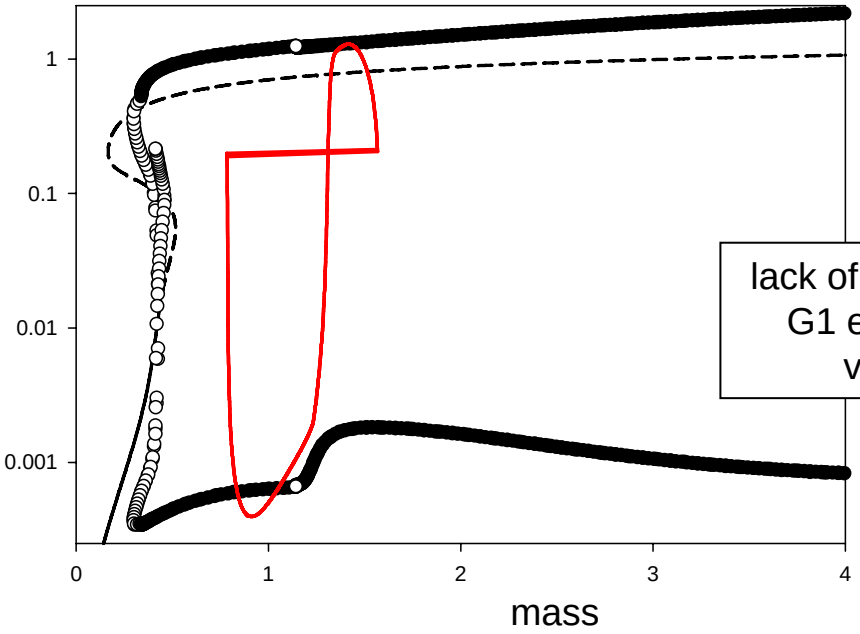

CycB
10^{1}
10^{0}
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^{-5}
G1
Period
time (min)
180
150
120
90
60
0
1
2
3
4
cell mass (au.)

Thesis 3.

Mutant phenotypes are direct consequences of altered bifurcation diagrams.

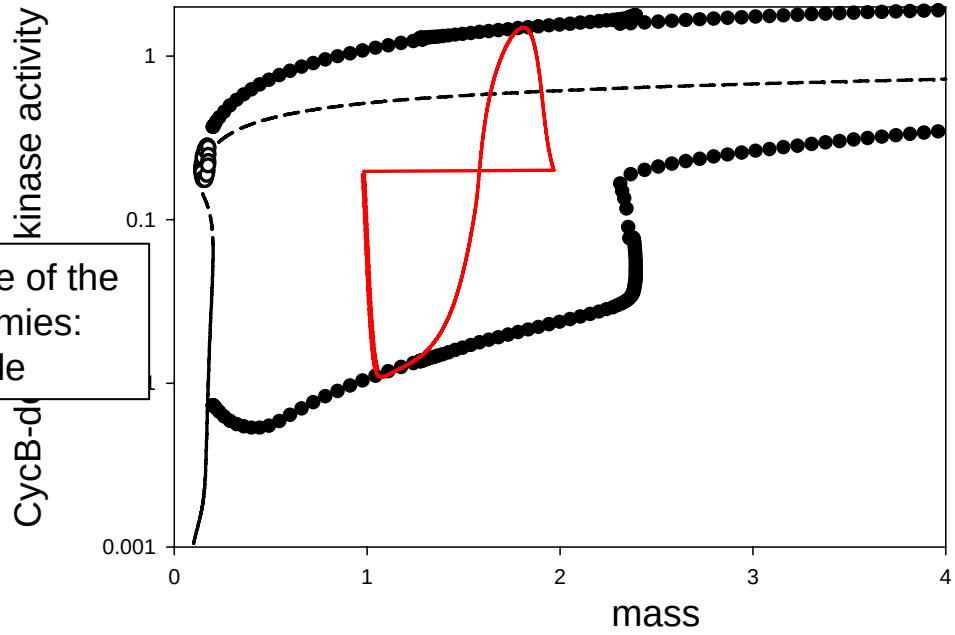

Wee1
P
Cdc14
Wee1
mass/nucleus
Cdc20
TFB$_A$
TFB$_I$
P
CycB
APC
APC-P
Cdc14
Cdc25
P
Cdc20
Cdc14
CycB
Cdh1
Cdc25
CKI
CycB
CycD
CycE
TFI$_I$
Cdh1
TFI$_A$
CycA
CycD
CKI
CKI
CycE
CKI
CycA
Cyc E,A,B
Cdc20
CycE
CycA
TFE$_A$
CycD
CycA
CycB
TFE$_I$

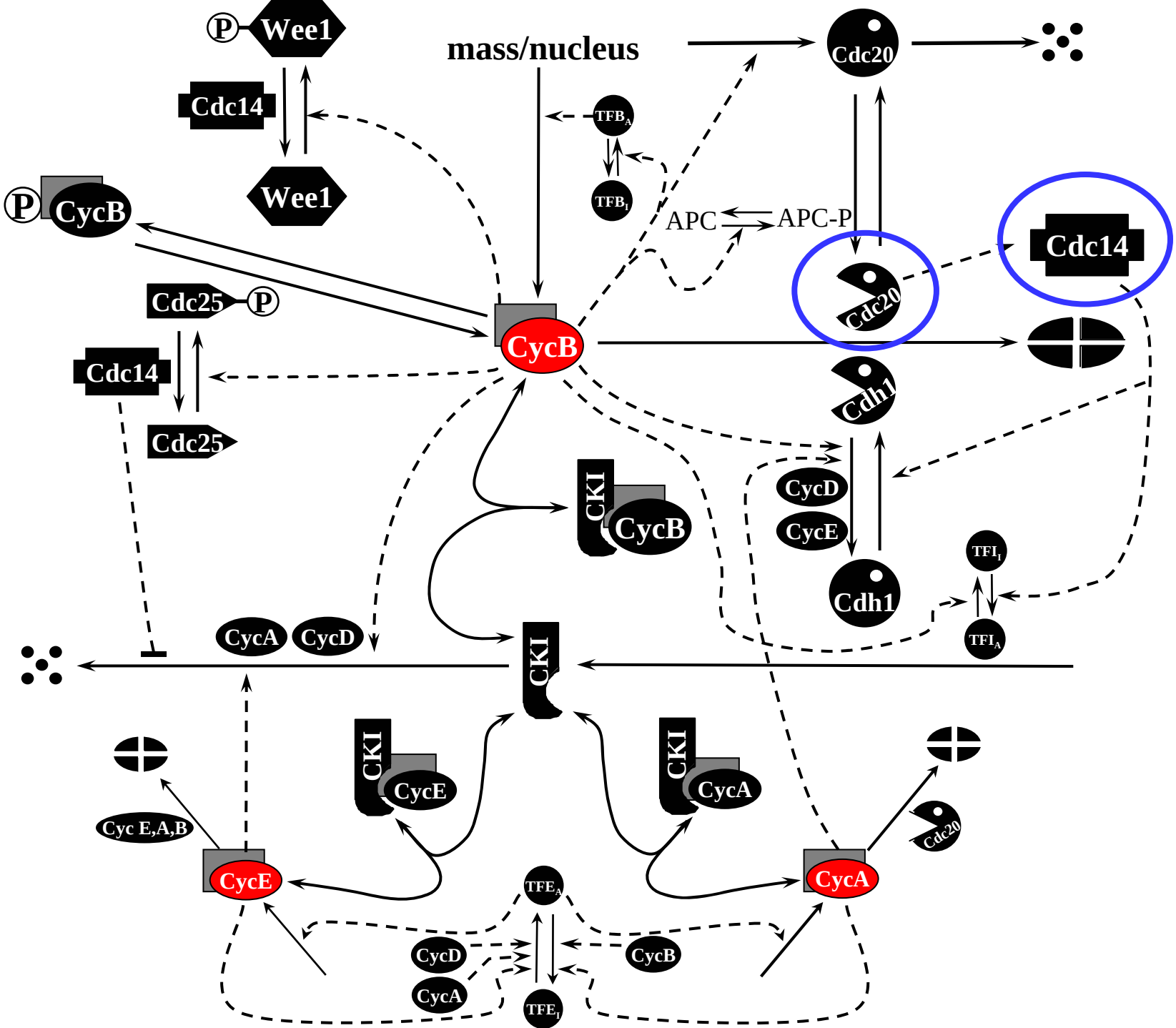
cdh1Δ



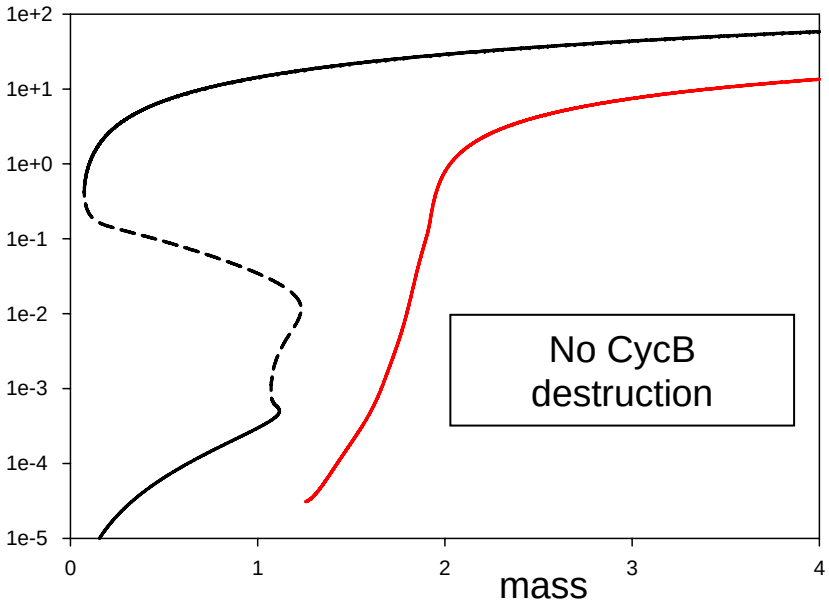
lack of one of the G1 enemies: viable

ckiΔ

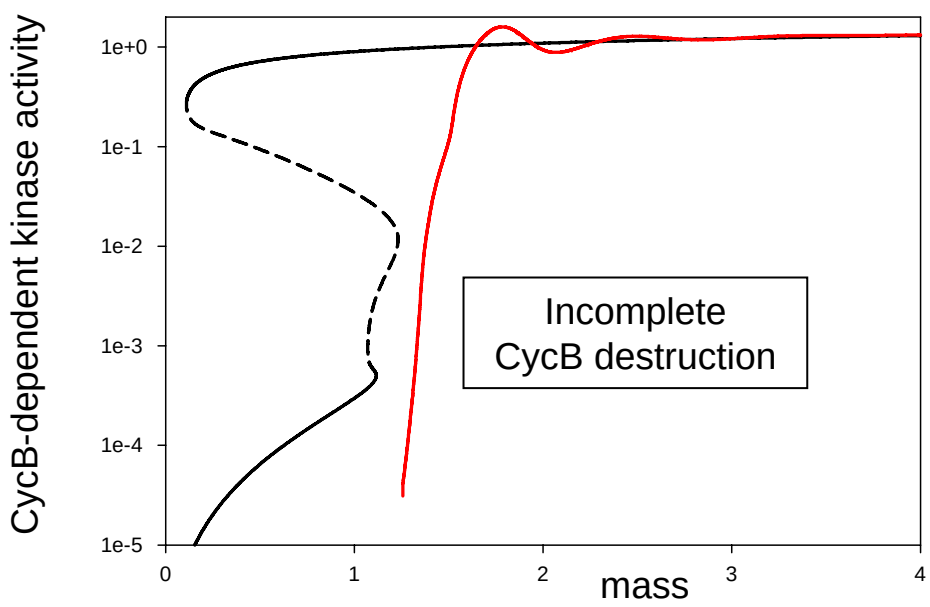



P
Wee1
Cdc14
Wee1
mass/nucleus
Cdc20
TFB$_A$
TFB$_I$
P
CycB
APC
APC-P
Cdc14
Cdc20
Cdc25
P
Cdc14
Cdc25
CycB
Cdh1
CKI
CycB
CycD
CycE
TFI$_I$
Cdh1
TFI$_A$
CycA
CycD
CKI
CKI
CycE
CKI
CycA
Cyc E,A,B
Cdc20
CycE
CycA
TFE$_A$
CycD
CycA
CycB
TFE$_I$

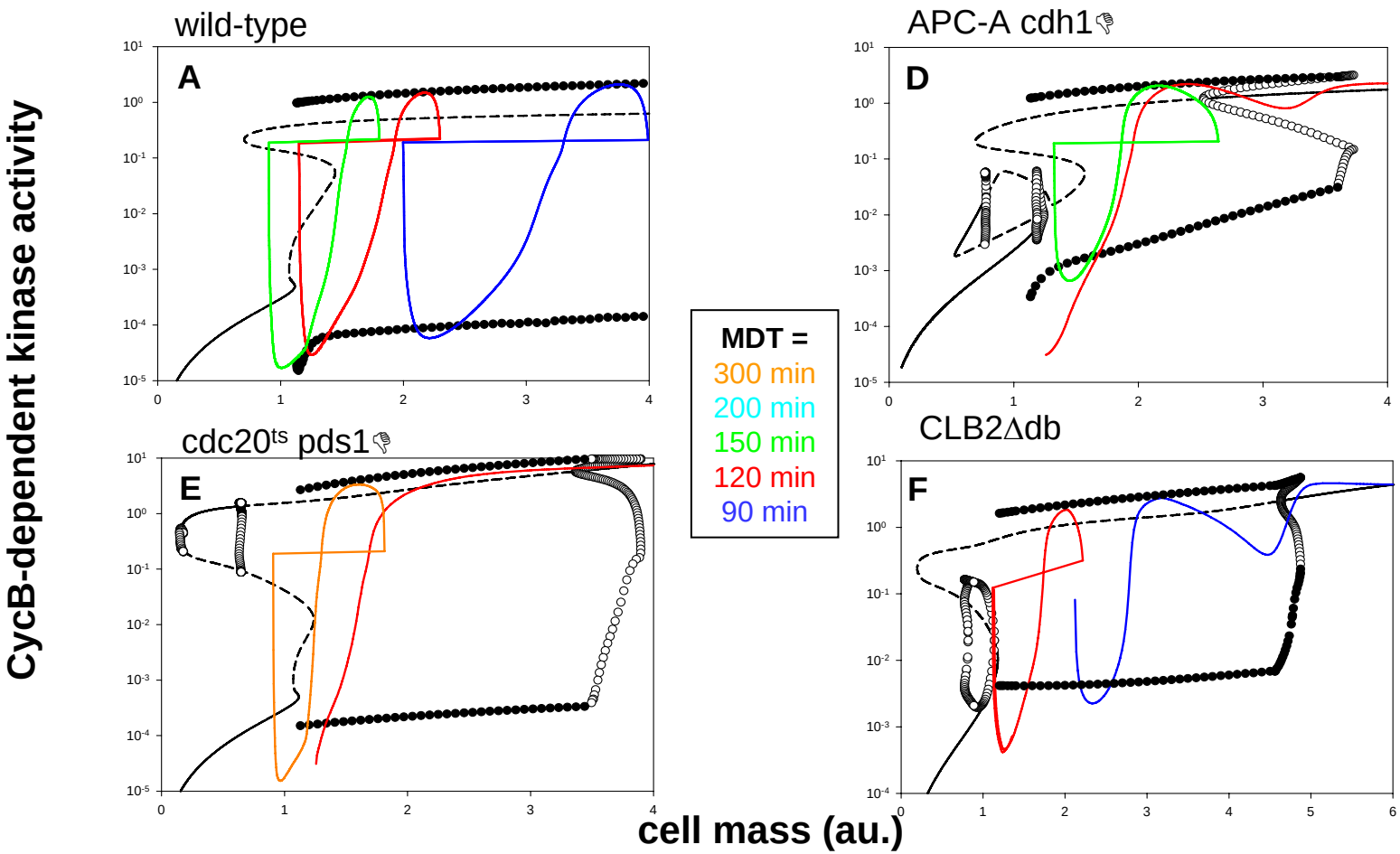
cdc20Δ



cdc14Δ



Defects in Exit from Mitosis

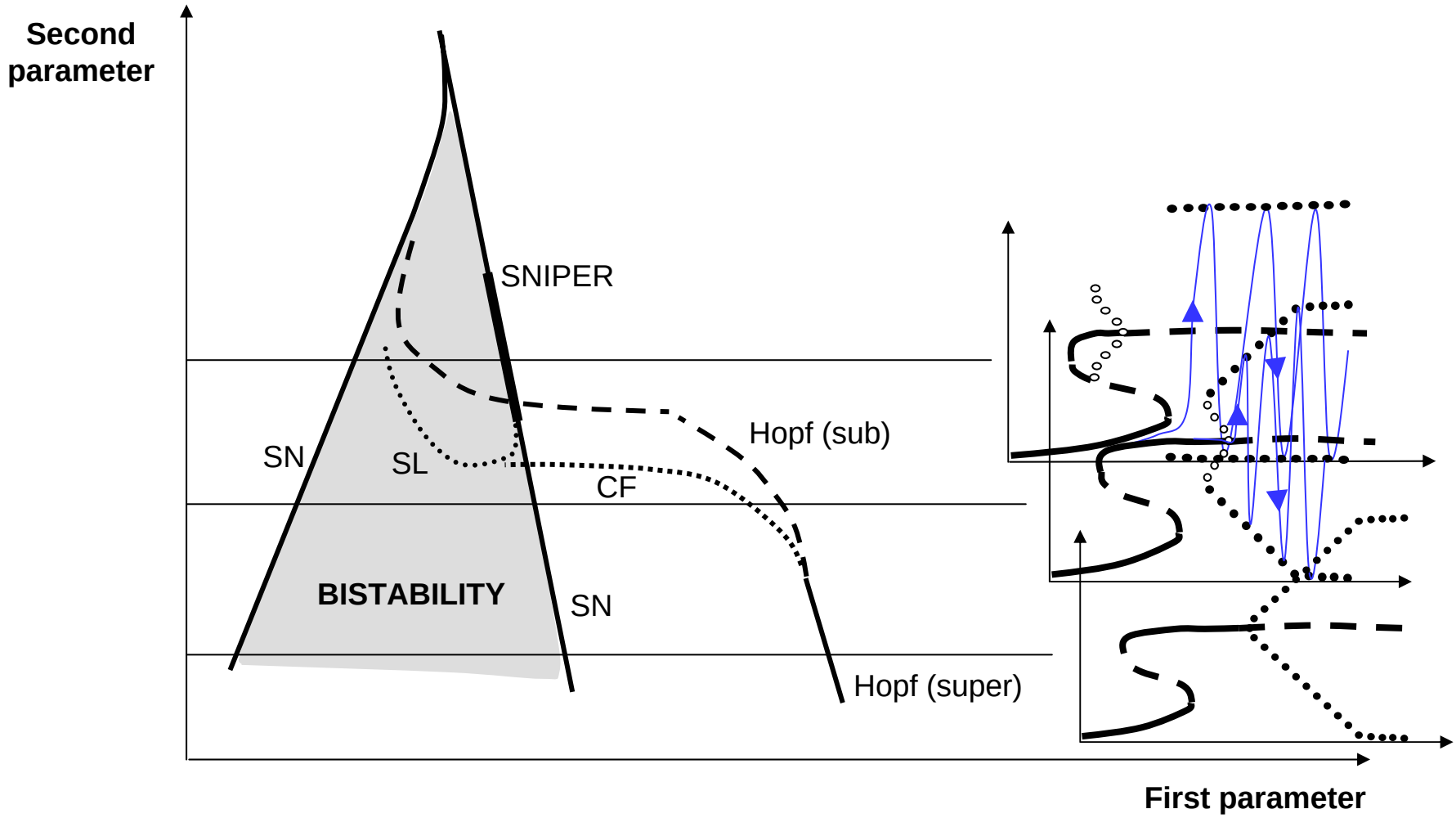


Viability depends on growth rate!

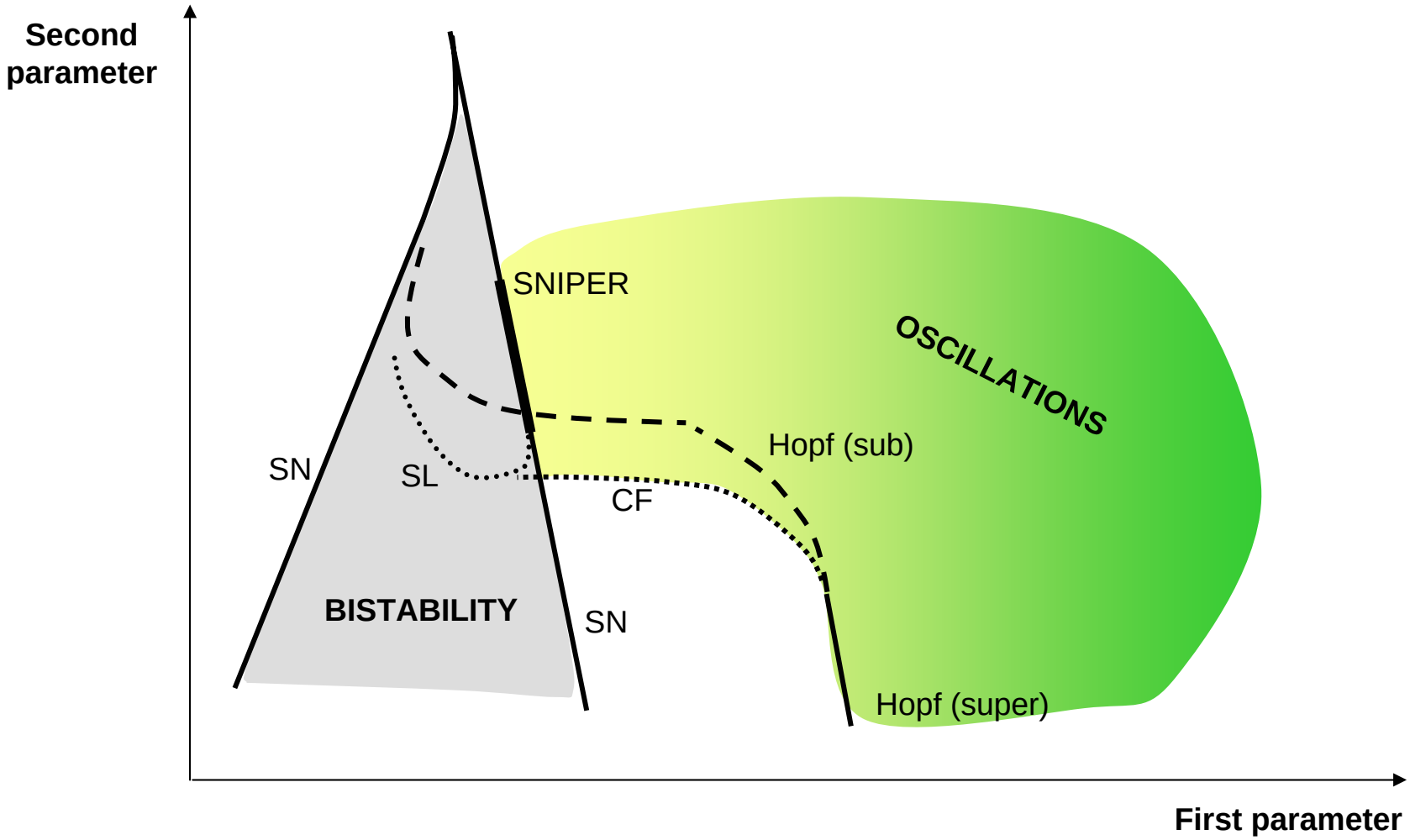
Thesis 4.

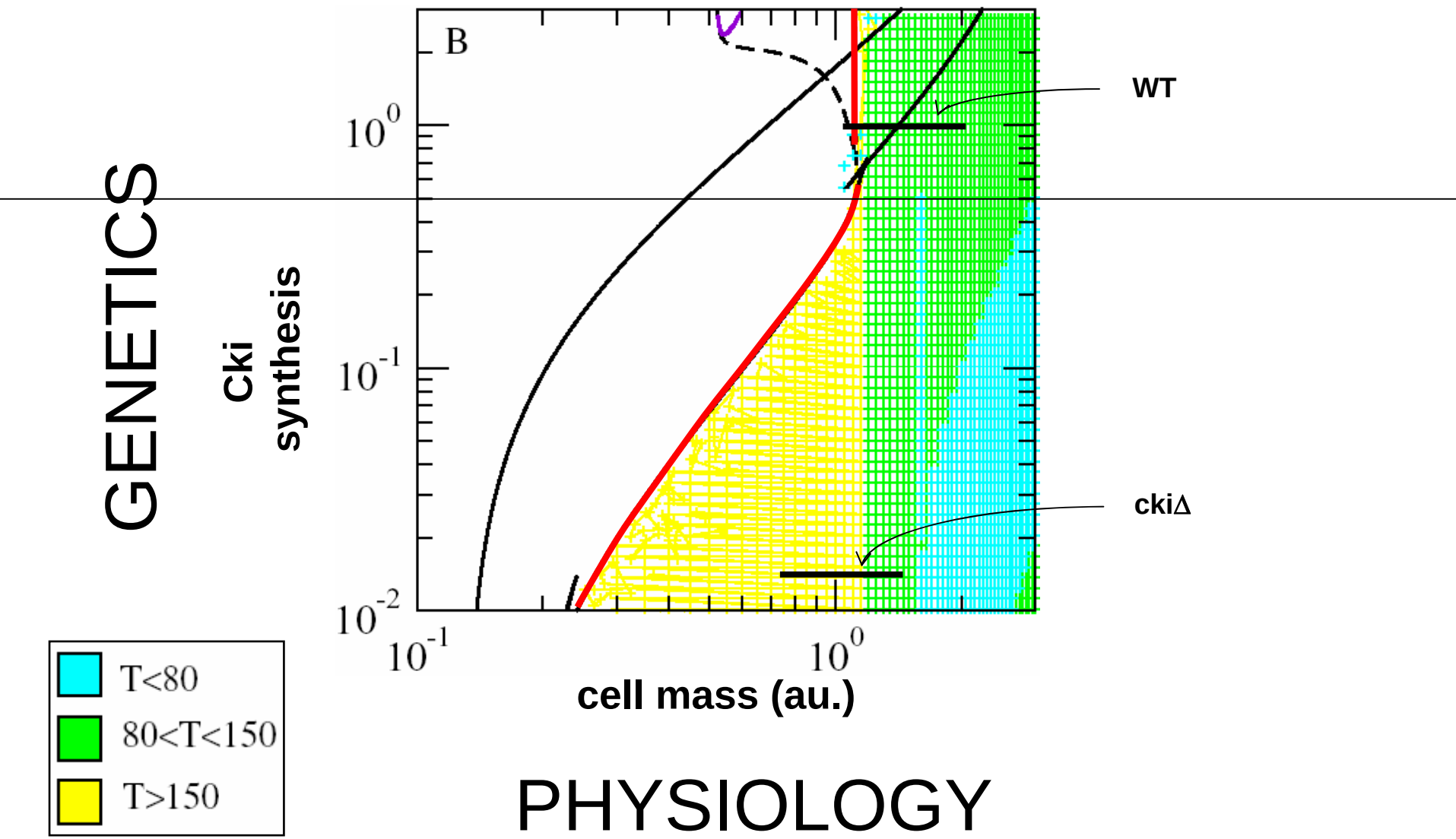
Two-parameter bifurcation diagrams connect genetics to physiology.

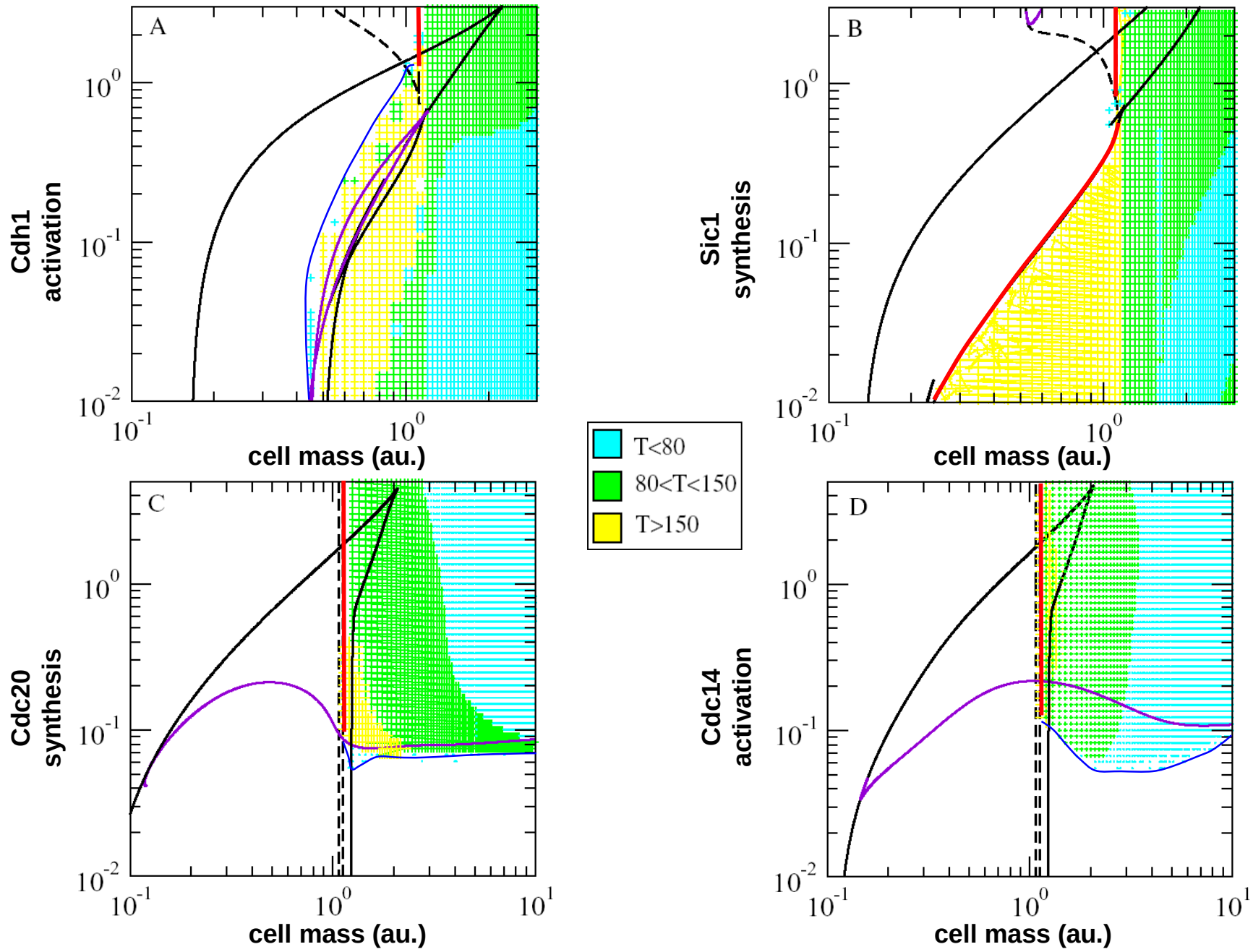
Two-parameter bifurcation diagram



Two-parameter bifurcation diagram

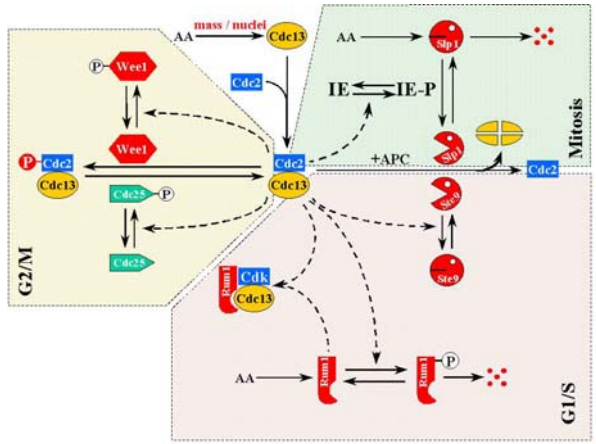



GENETICS
Cki
synthesis
B
10^0
10^{-1}
10^{-2}
10^{-1}
10^0
cell mass (au.)
WT
ckiΔ
T<80
80<T<150
T>150
PHYSIOLOGY


A
B
C
D
Cdh1 activation
Sic1 synthesis
Cdc20 synthesis
Cdc14 activation
cell mass (au.)
T<80
80<T<150
T>150

The Dynamical Perspective

Molecular Mechanism



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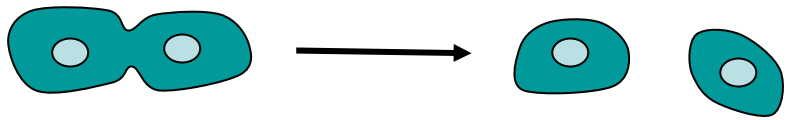
Physiological Properties



The Dynamical Perspective

Molecular Mechanism

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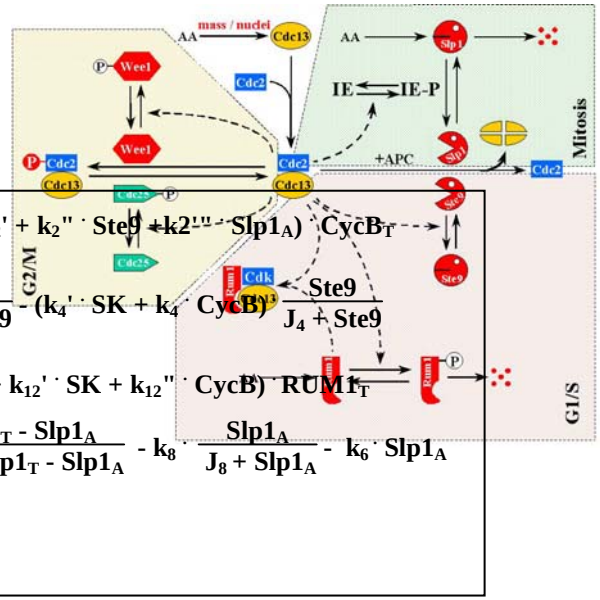
Kinetic Equations



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

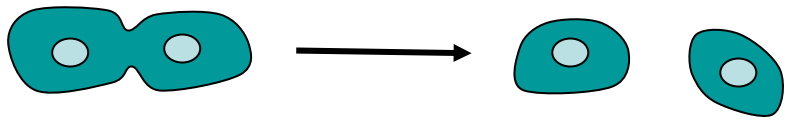
$$\frac{dSte9}{dt} = k_3' \cdot \frac{1 - Ste9}{J_3 + 1 - Ste9} - (k_4' \cdot SK + k_4 \cdot CycB) \frac{Ste9}{J_4 + Ste9}$$

$$\frac{d\,Rum1_T}{dt} = k_{11} - (k_{12} + k_{12}' \cdot SK + k_{12}'' \cdot CycB) \cdot RUM1_T$$

$$\frac{dSlp1_A}{dt} = k_7 \cdot IE \cdot \frac{Slp1_T - Slp1_A}{J_7 + Slp1_T - Slp1_A} - k_8 \cdot \frac{Slp1_A}{J_8 + Slp1_A} - k_6 \cdot Slp1_A$$

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

Physiological Properties



The Dynamical Perspective

Molecular Mechanism

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Kinetic Equations

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Vector Field

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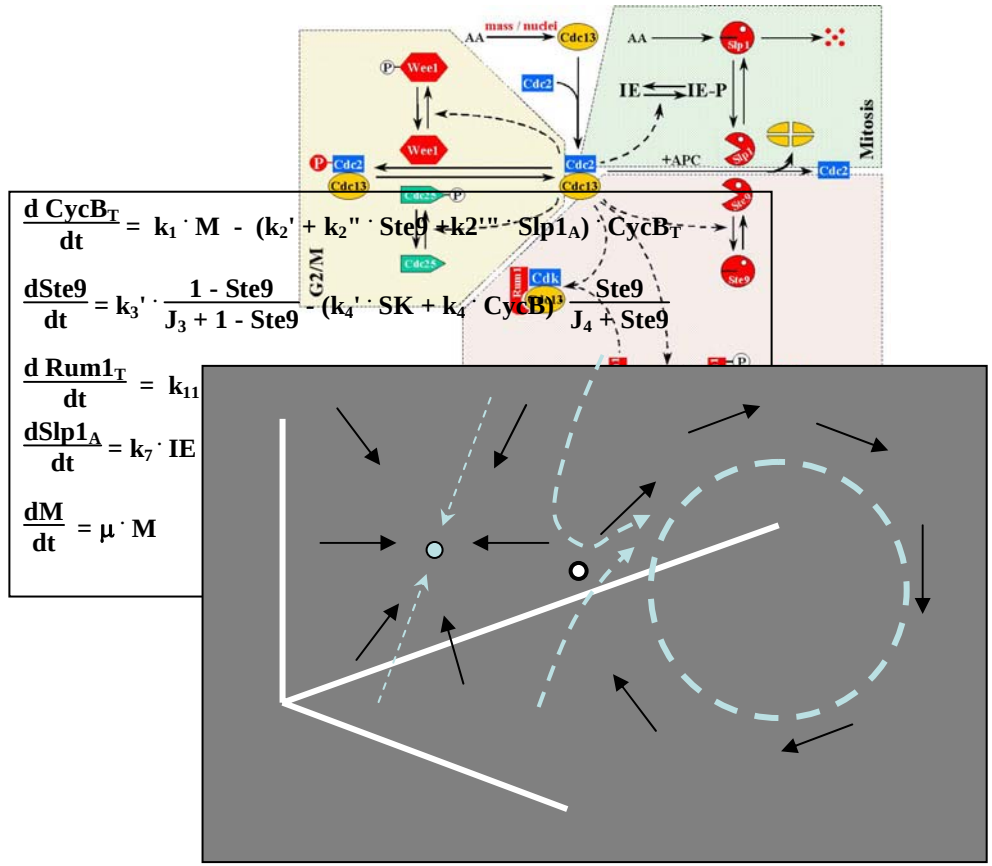
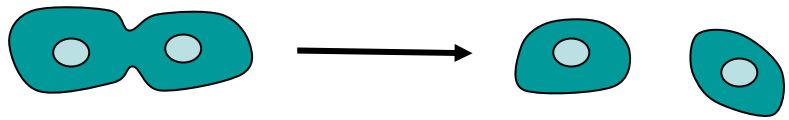
Stable Attractors



Physiological Properties



The Dynamical Perspective

Molecular Mechanism

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Kinetic Equations

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Vector Field

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Stable Attractors

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Bifurcations

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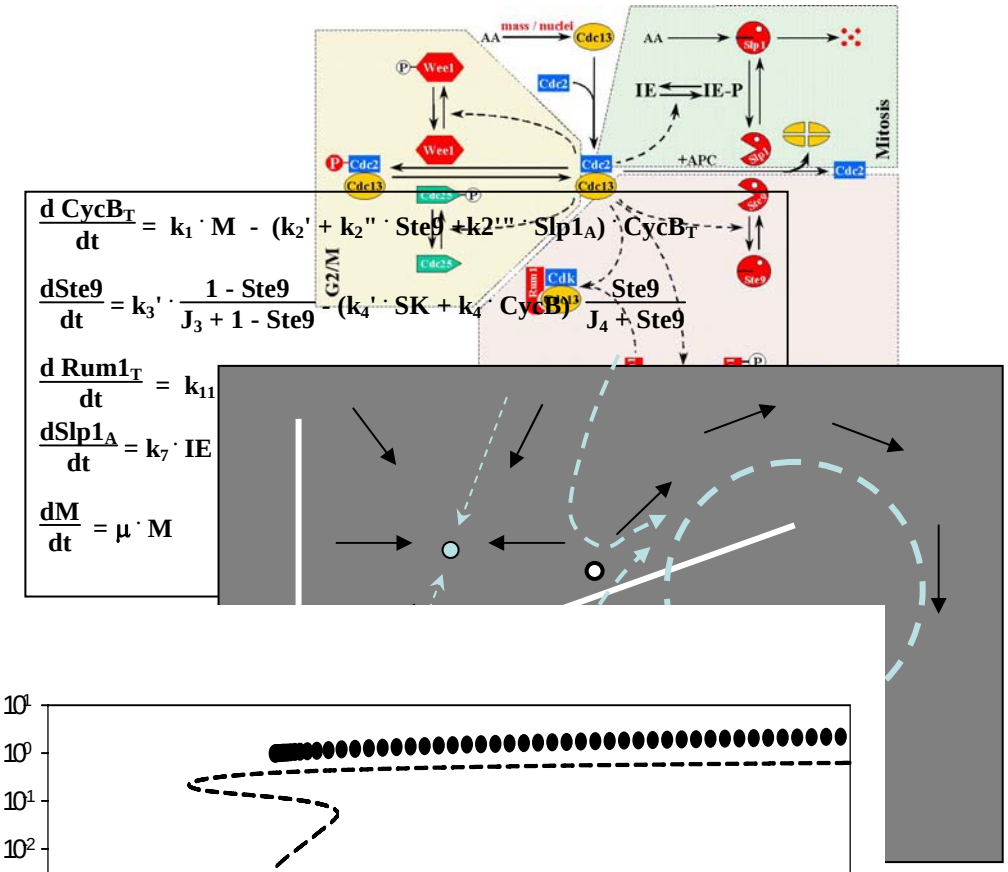
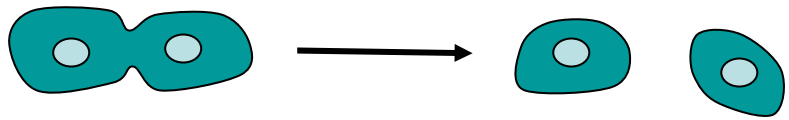
Physiological Properties





The Dynamical Perspective

Molecular Mechanism

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Kinetic Equations

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Vector Field

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Stable Attractors

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Bifurcations

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Physiological Properties