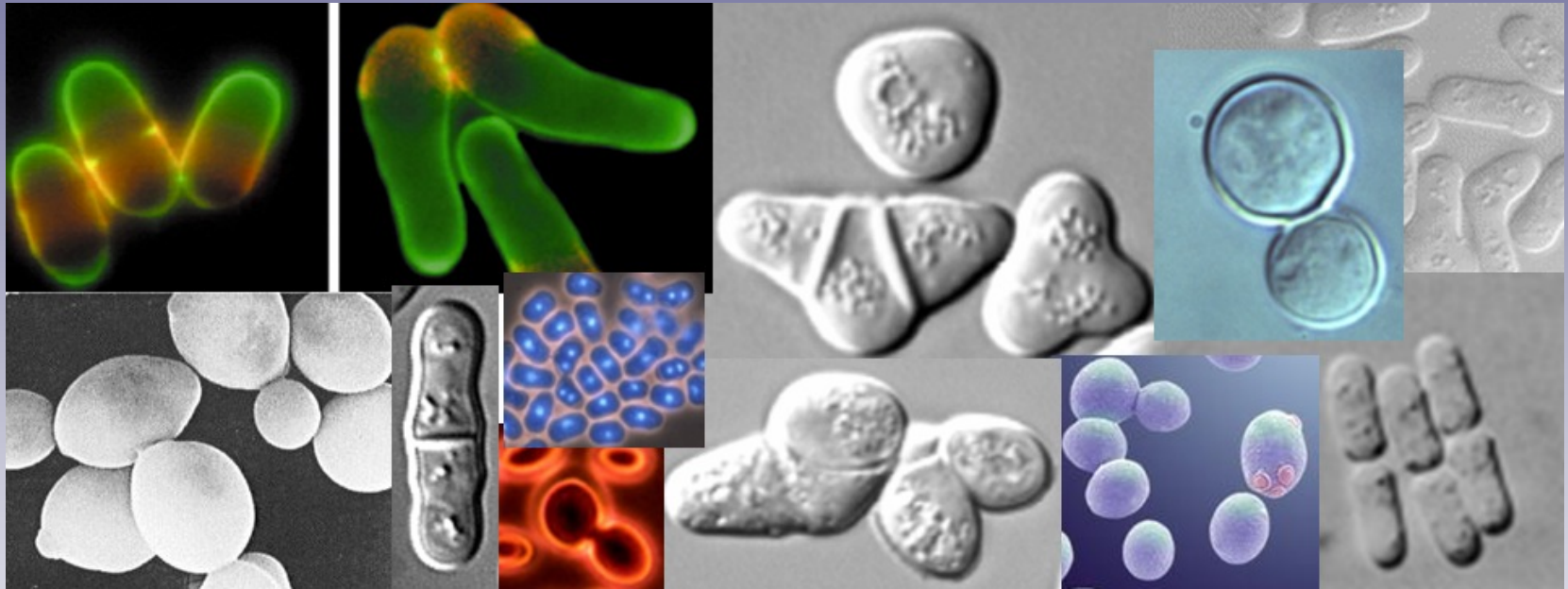


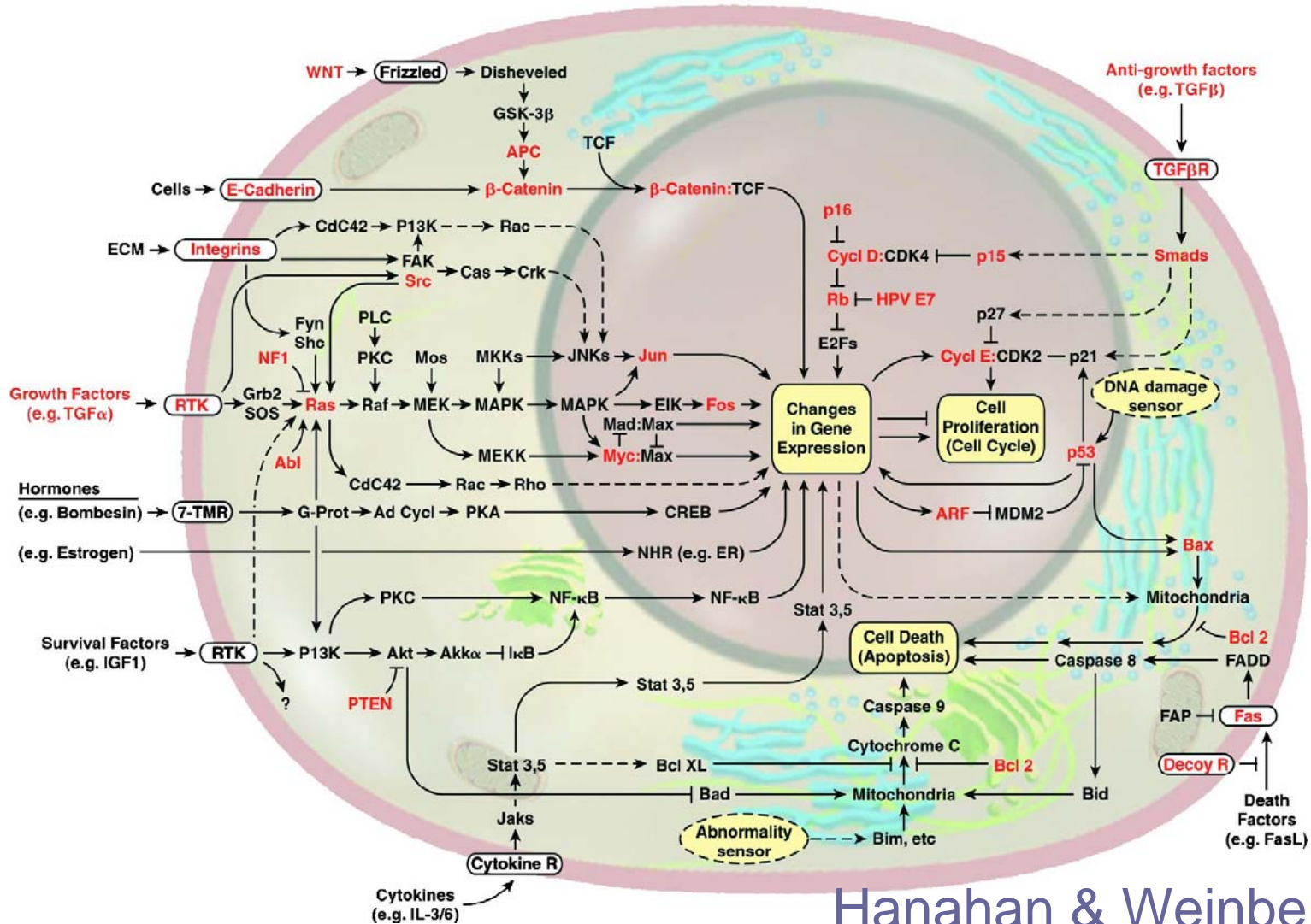
Network Dynamics and Cell Physiology



John J. Tyson

Department of Biological Sciences
& Virginia Bioinformatics Institute

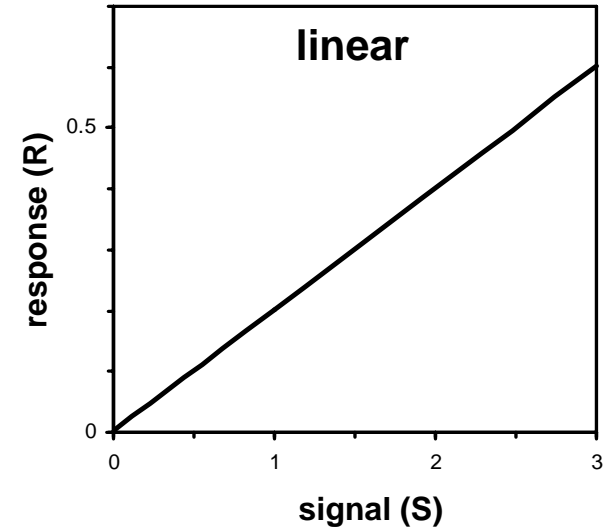
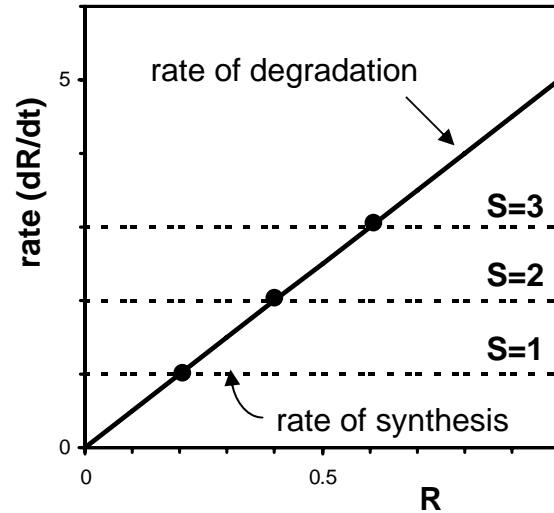
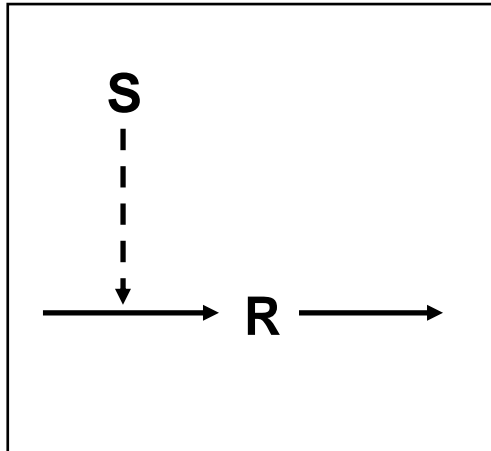
Signal Transduction Network



Hanahan & Weinberg (2000)

Gene Expression

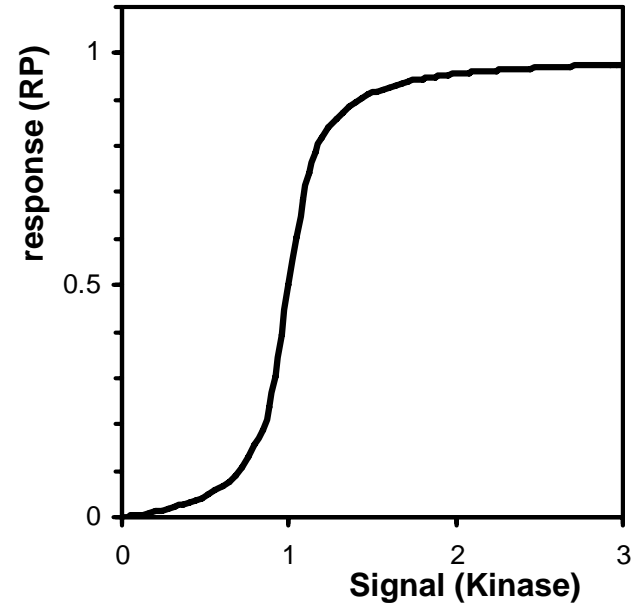
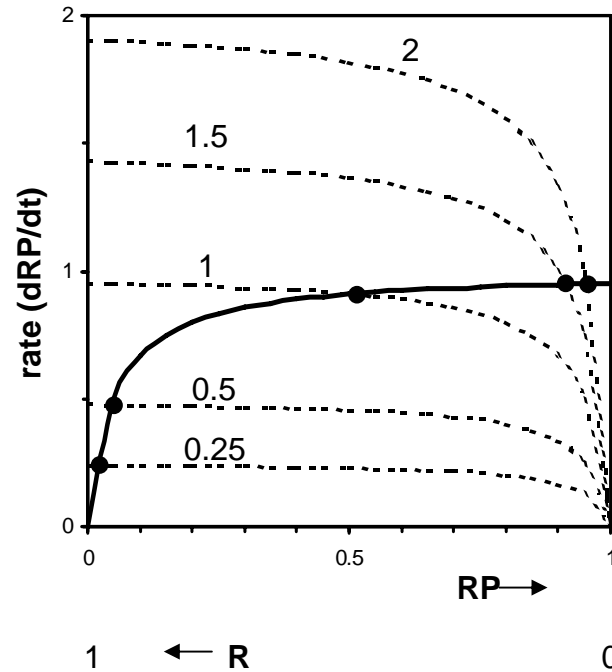
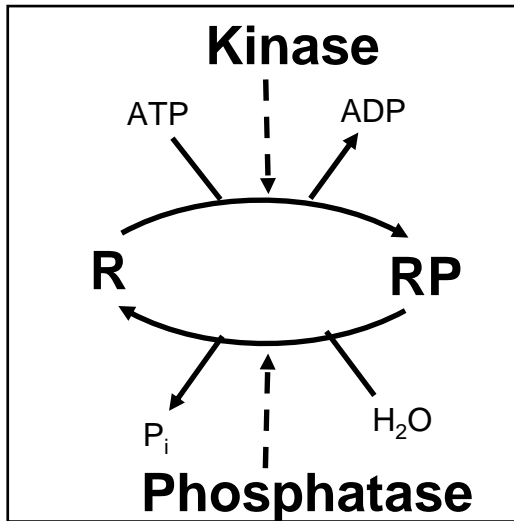
Signal-Response Curve



$$\frac{dR}{dt} = k_1 S - k_2 R, \quad R_{ss} = \frac{k_1 S}{k_2}$$

“Lever”

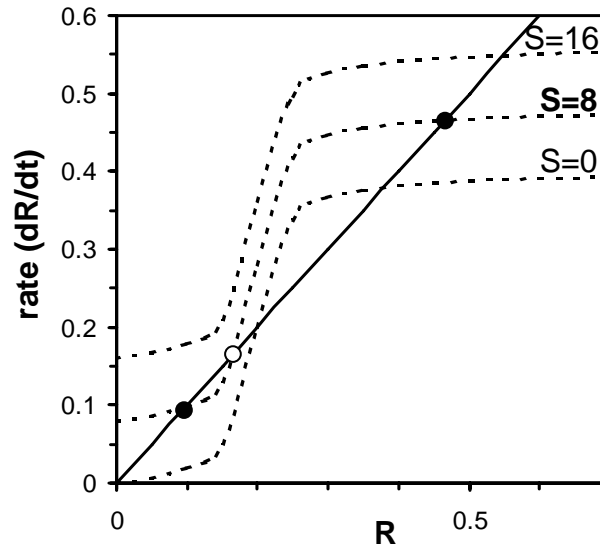
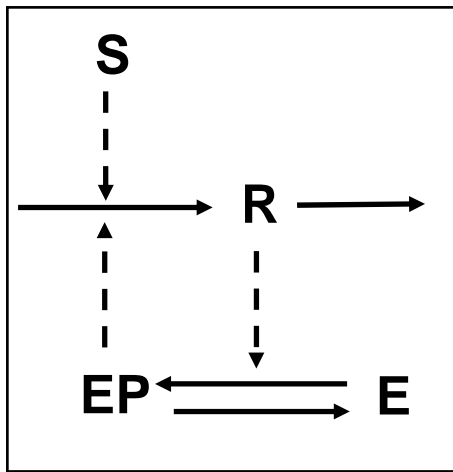
Protein Phosphorylation



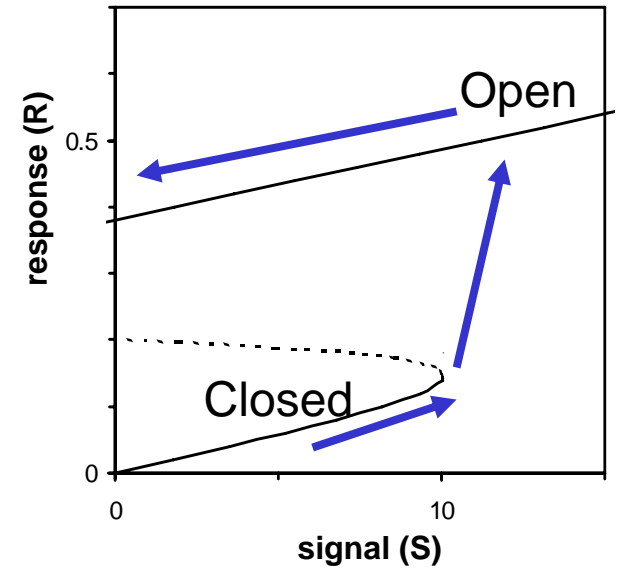
“Buzzer”

Goldbeter & Koshland (1981)

Protein Synthesis: Positive Feedback

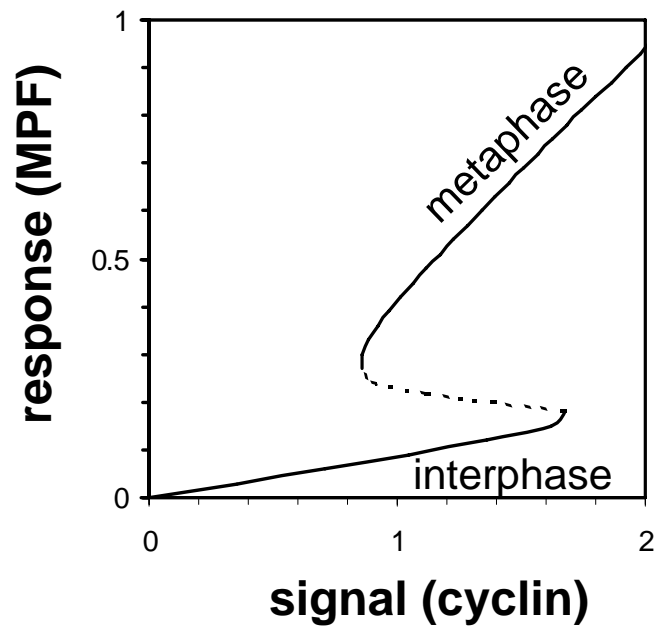
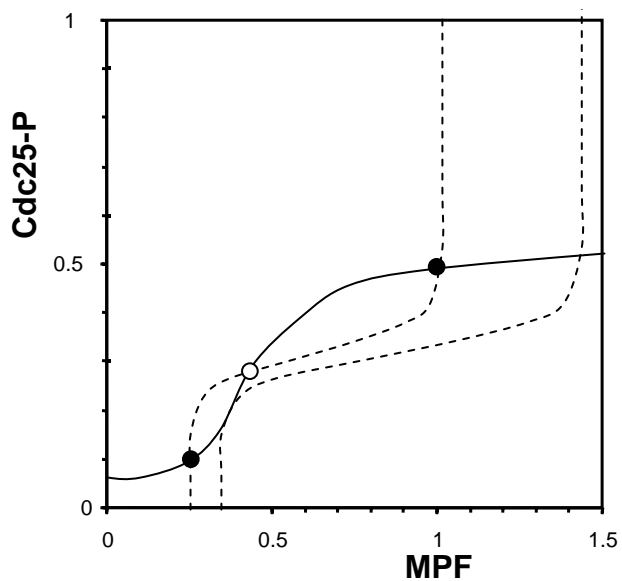
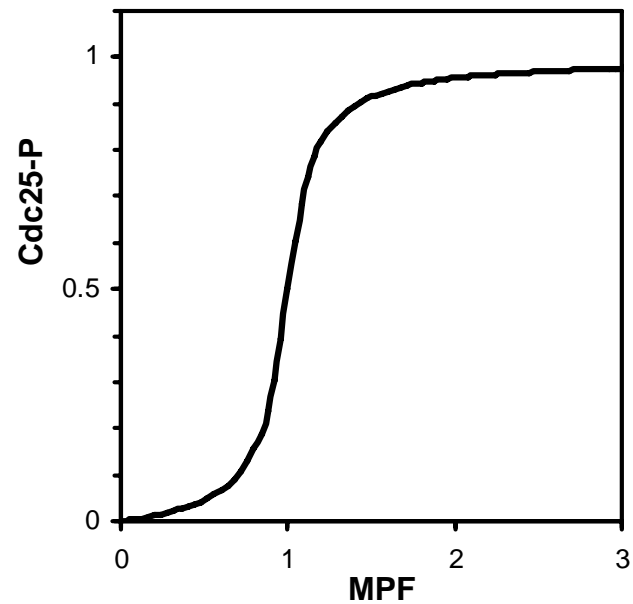
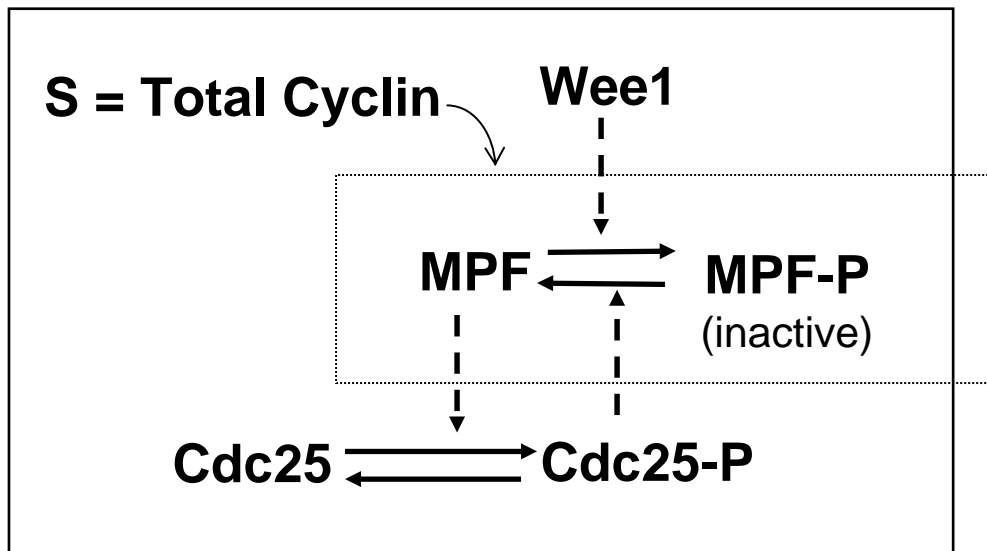


Bistability



“Fuse”

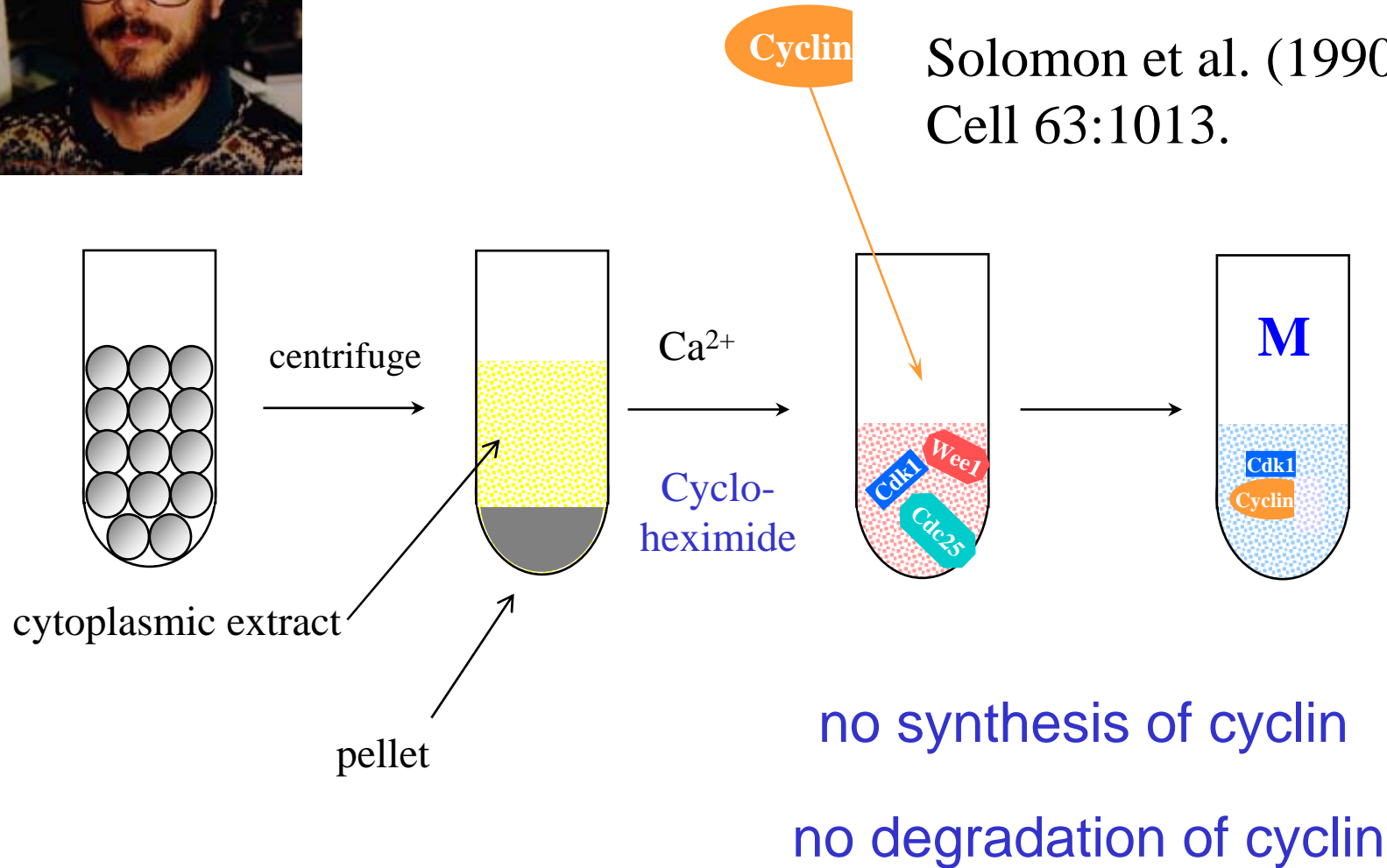
Griffith (1968)



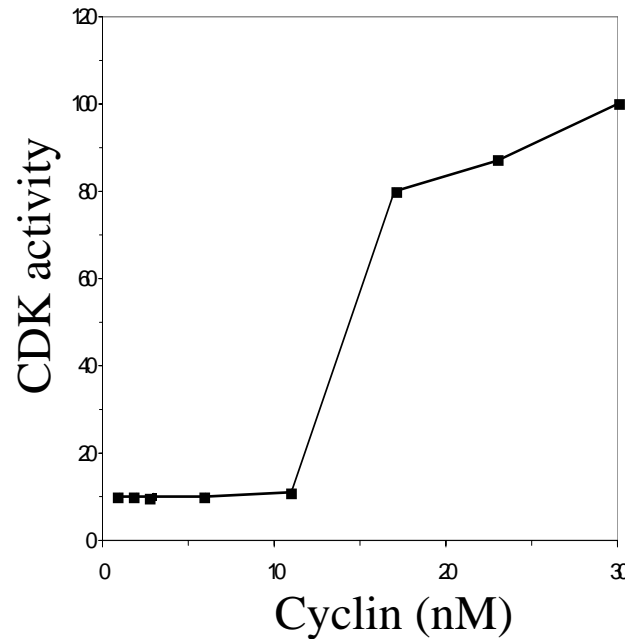


Solomon's protocol for cyclin-induced activation of MPF

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



Threshold



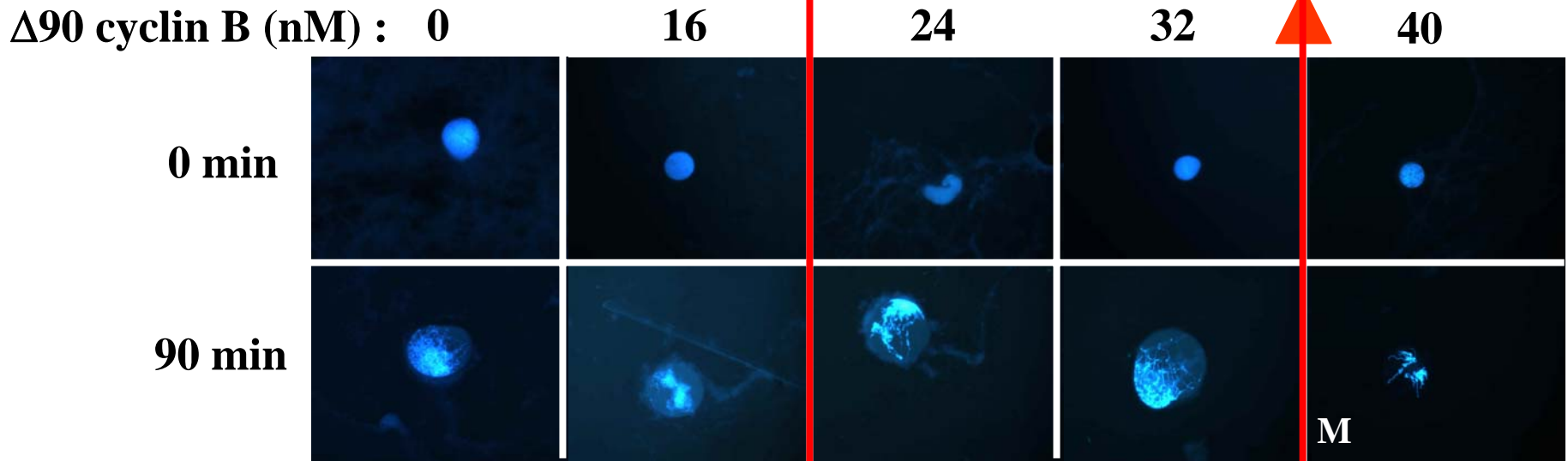
Solomon et al. (1990)
Cell 63:1013.

Novak & Tyson (1993)
J. Cell Sci. **106**:1153

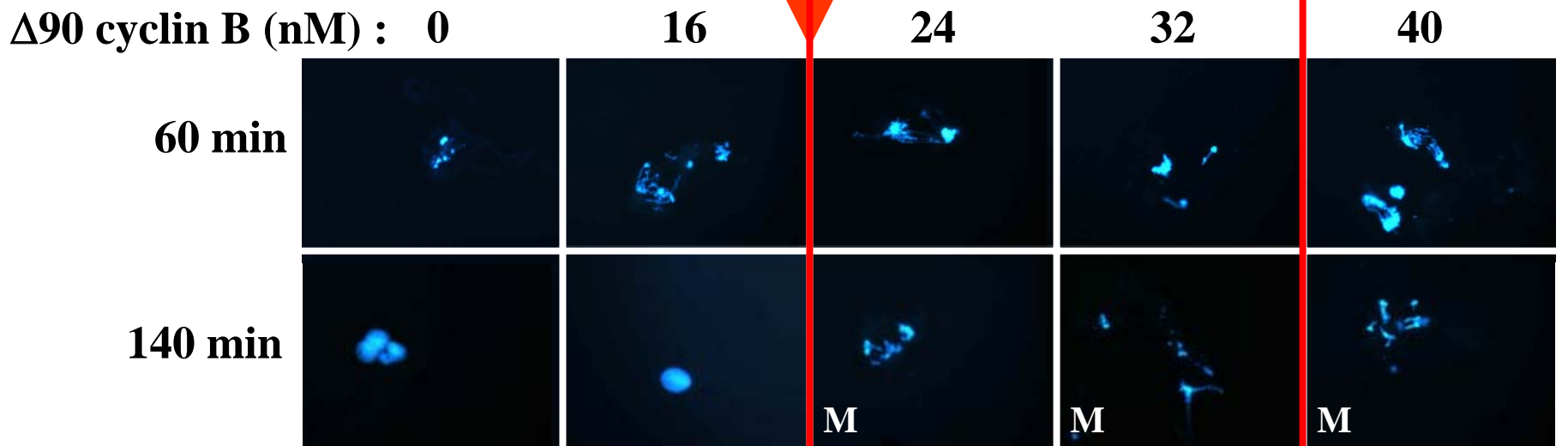
Sha et al., PNAS 100:975-980 (2003)

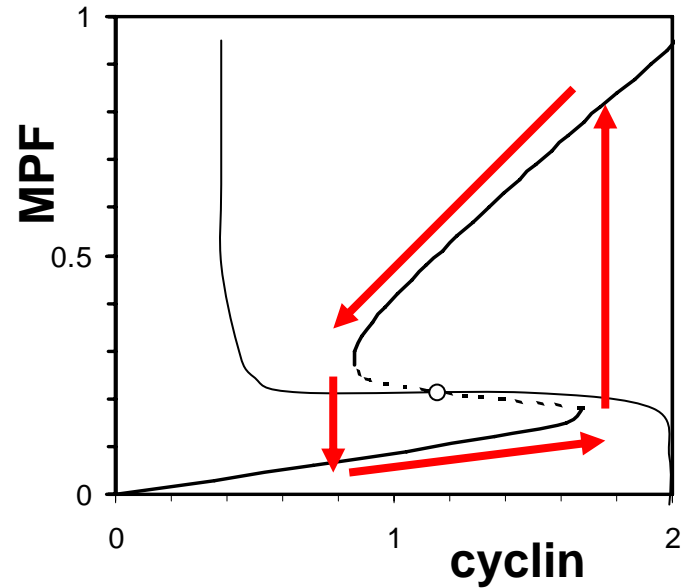
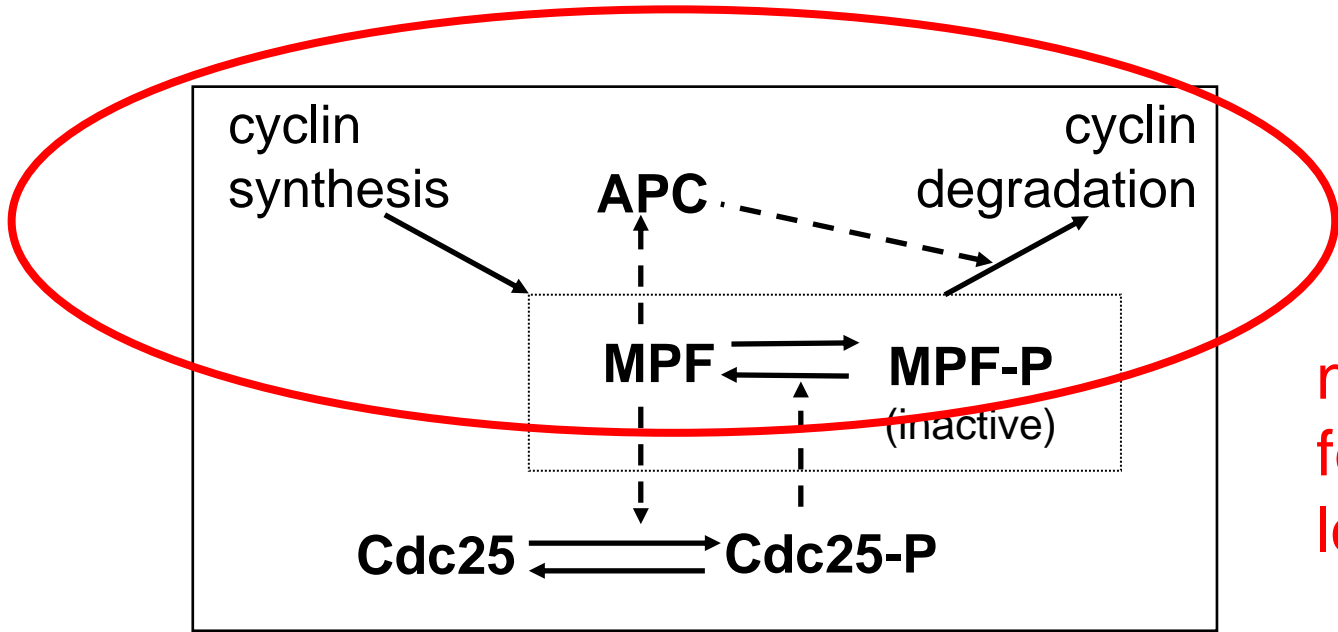
Pomerening et al., Nature Cell Biology 5:346-351 (2003)

The activation threshold for Mitosis I is between 32 and 40 nM.



The inactivation threshold for Mitosis I is between 16 and 24 nM.





Pomerening, Kim & Ferrell Cell (2005)

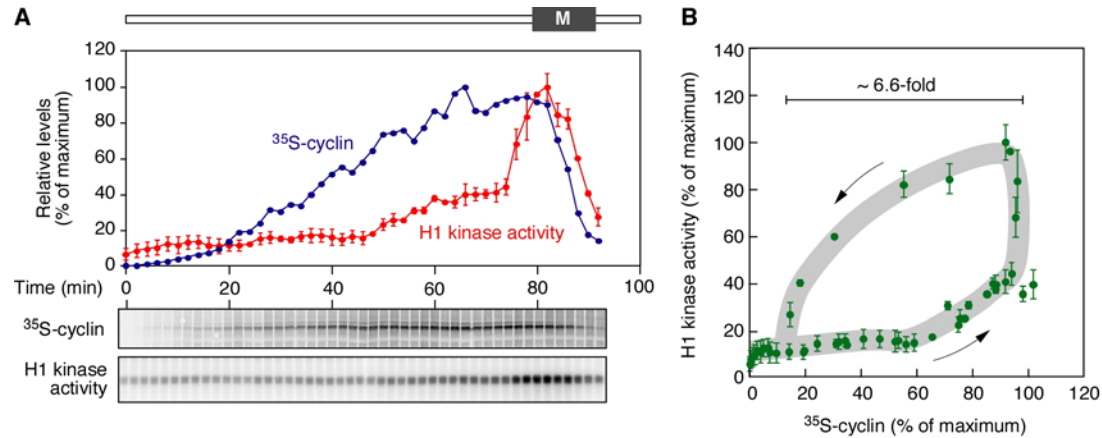
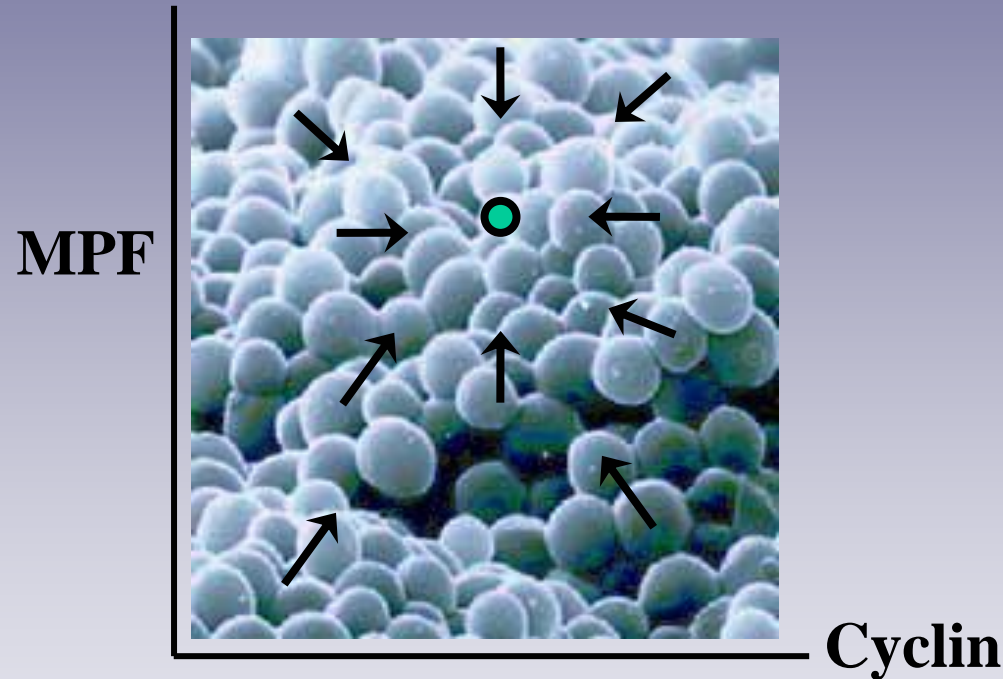
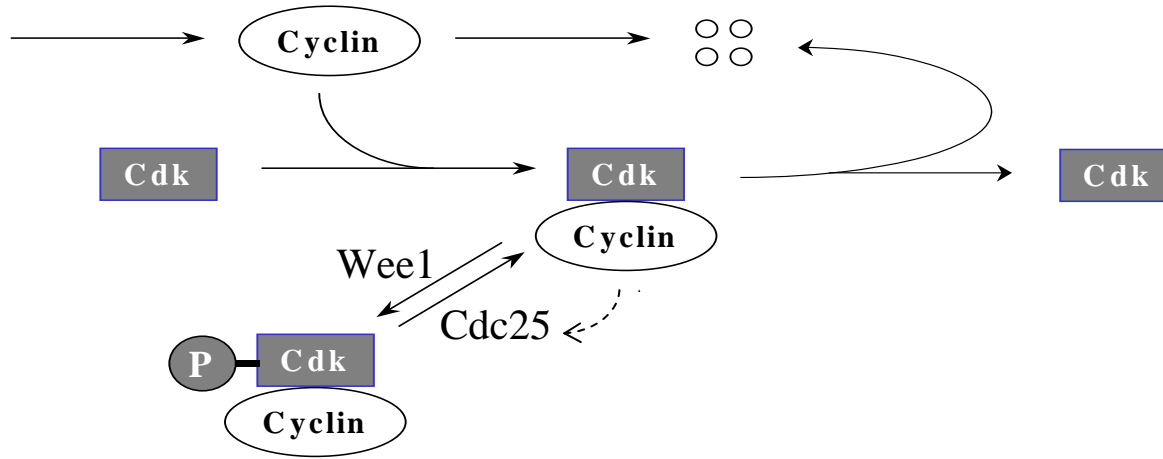


Figure 3
Pomerening, Kim and Ferrell

Dynamical Perspective on Molecular Cell Biology

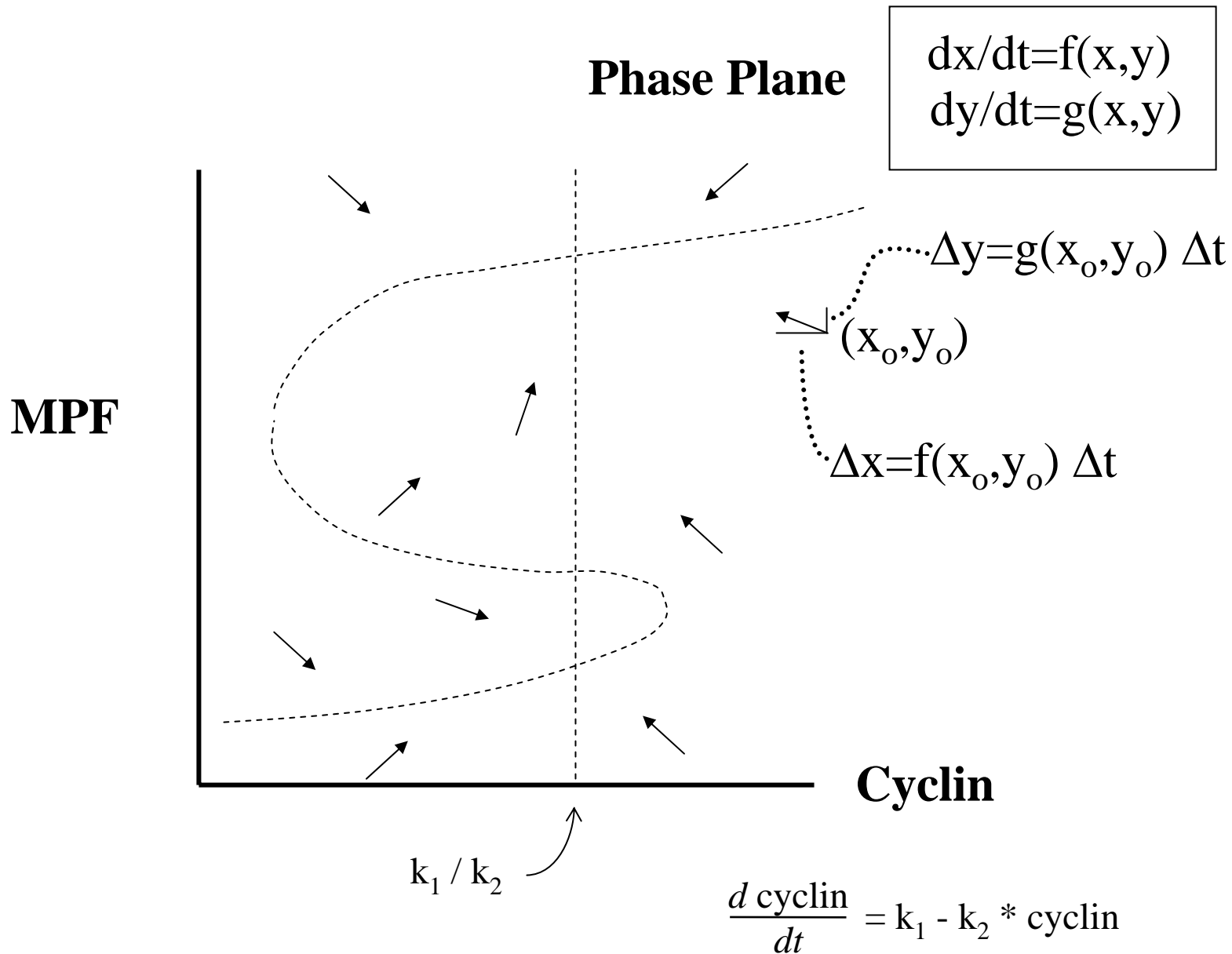


Vector Field, Steady State, Bifurcation



$$\frac{d \text{MPF}}{dt} = k_1 - (k_{\text{wee}} + k_2) * \text{MPF} + k_{25} (\text{cyclin} - \text{MPF})$$

$$\frac{d \text{cyclin}}{dt} = k_1 - k_2 * \text{cyclin}$$

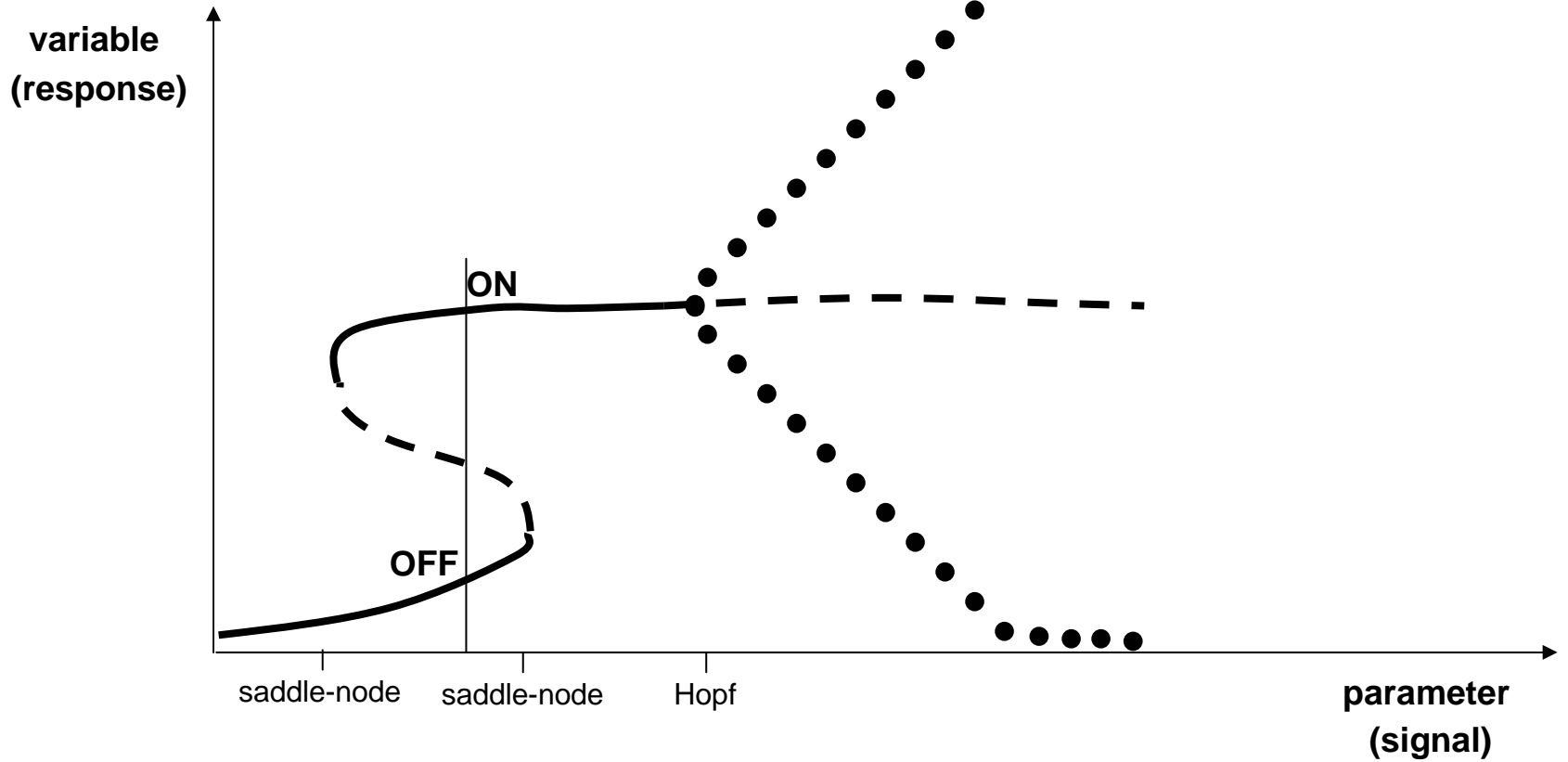


One-parameter bifurcation diagram



Signal

Response

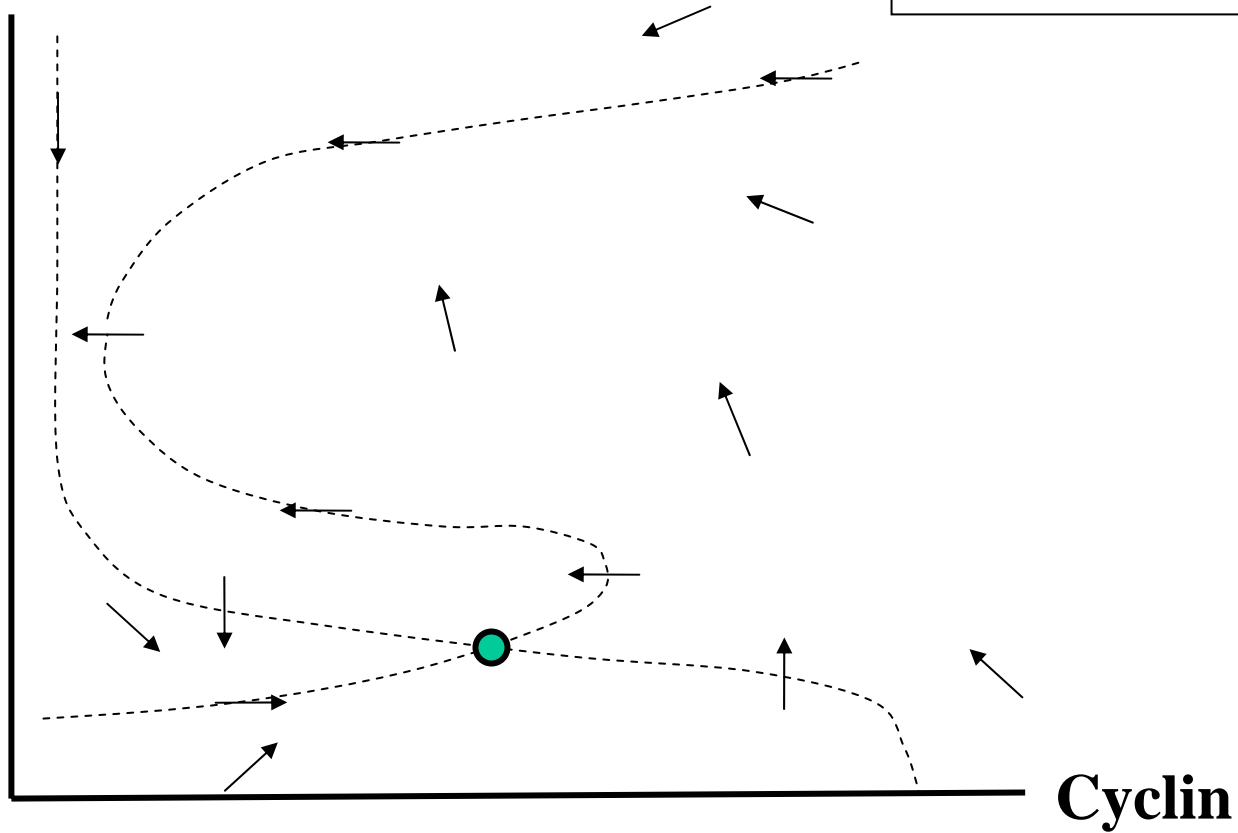


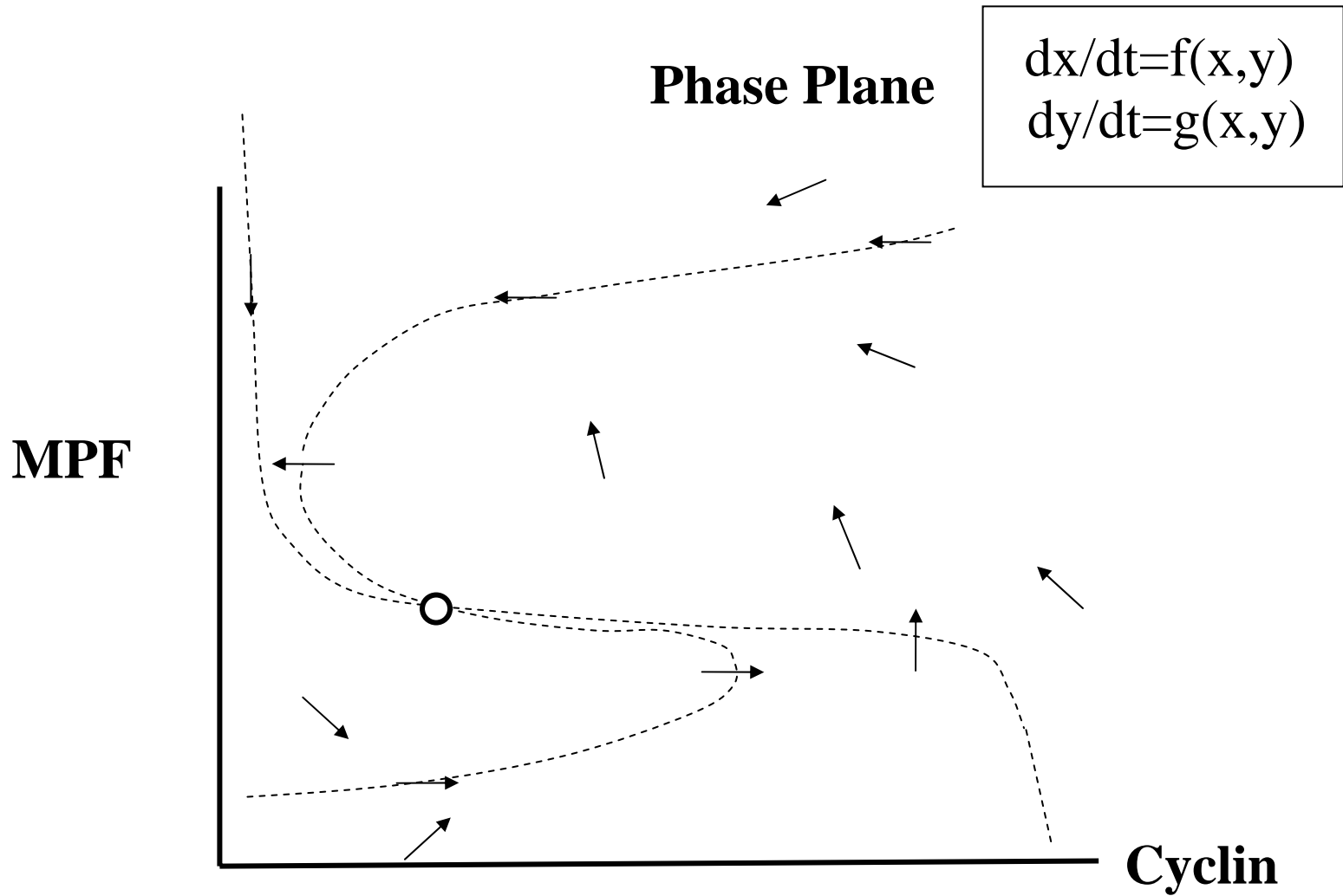
- stable steady state
- - - unstable steady state

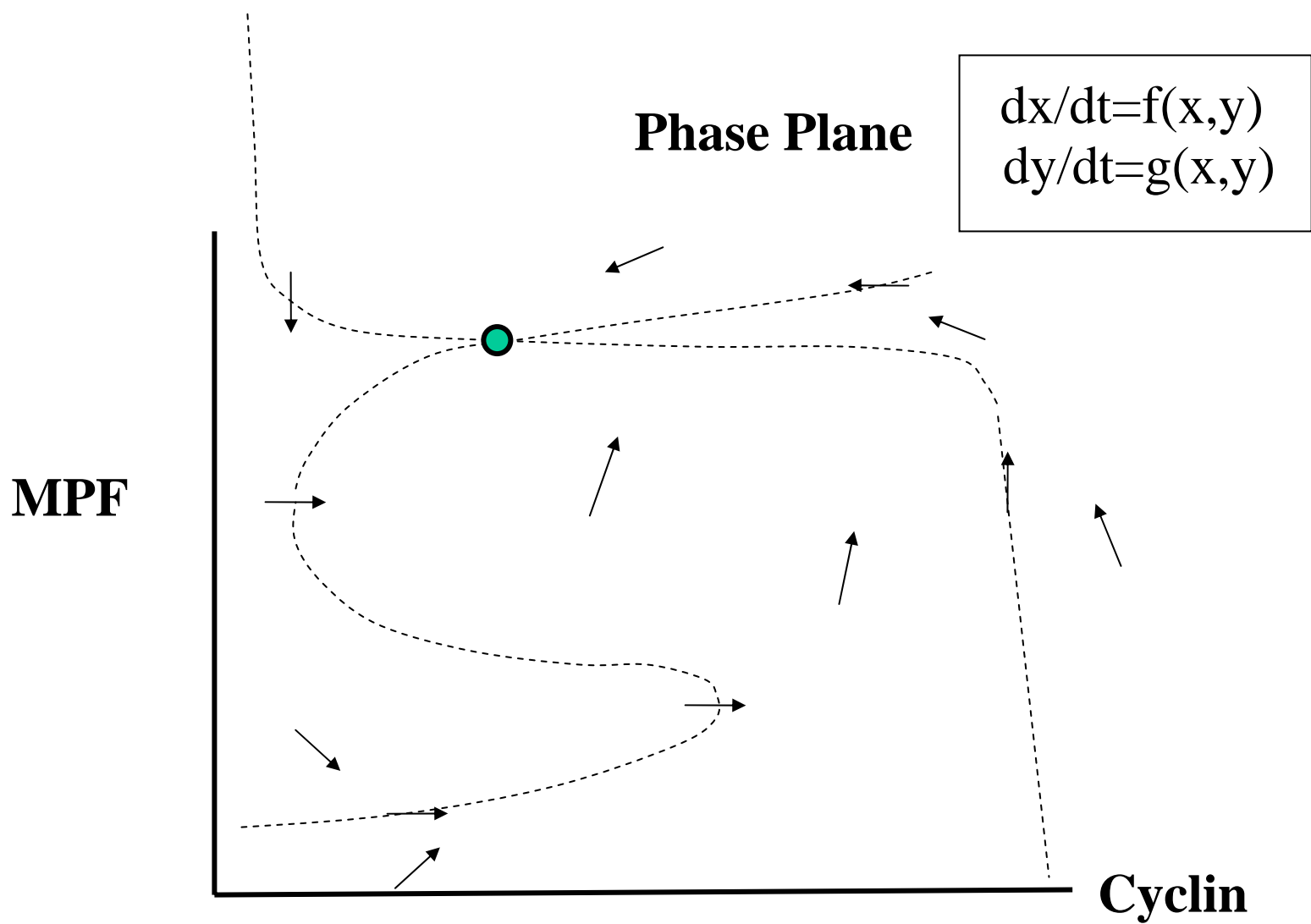
Phase Plane

$$\begin{aligned} dx/dt &= f(x,y) \\ dy/dt &= g(x,y) \end{aligned}$$

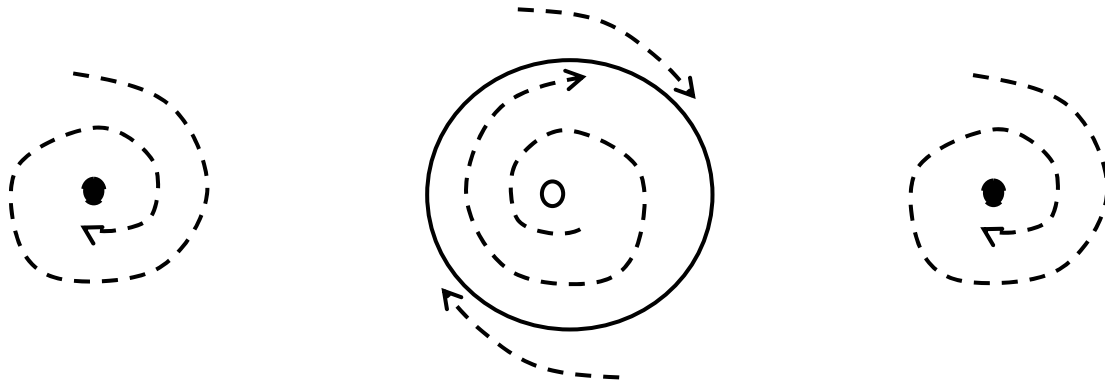
MPF

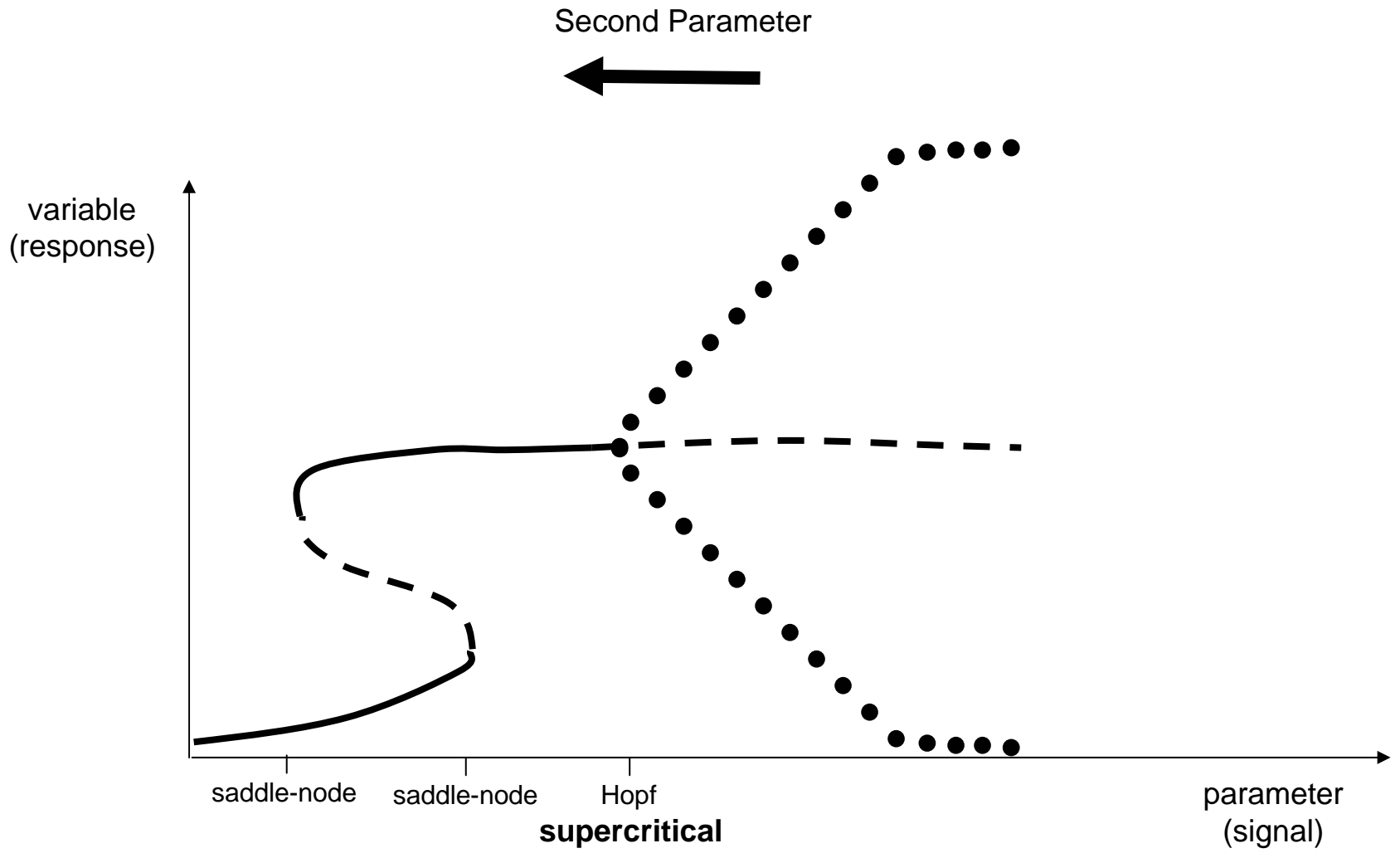


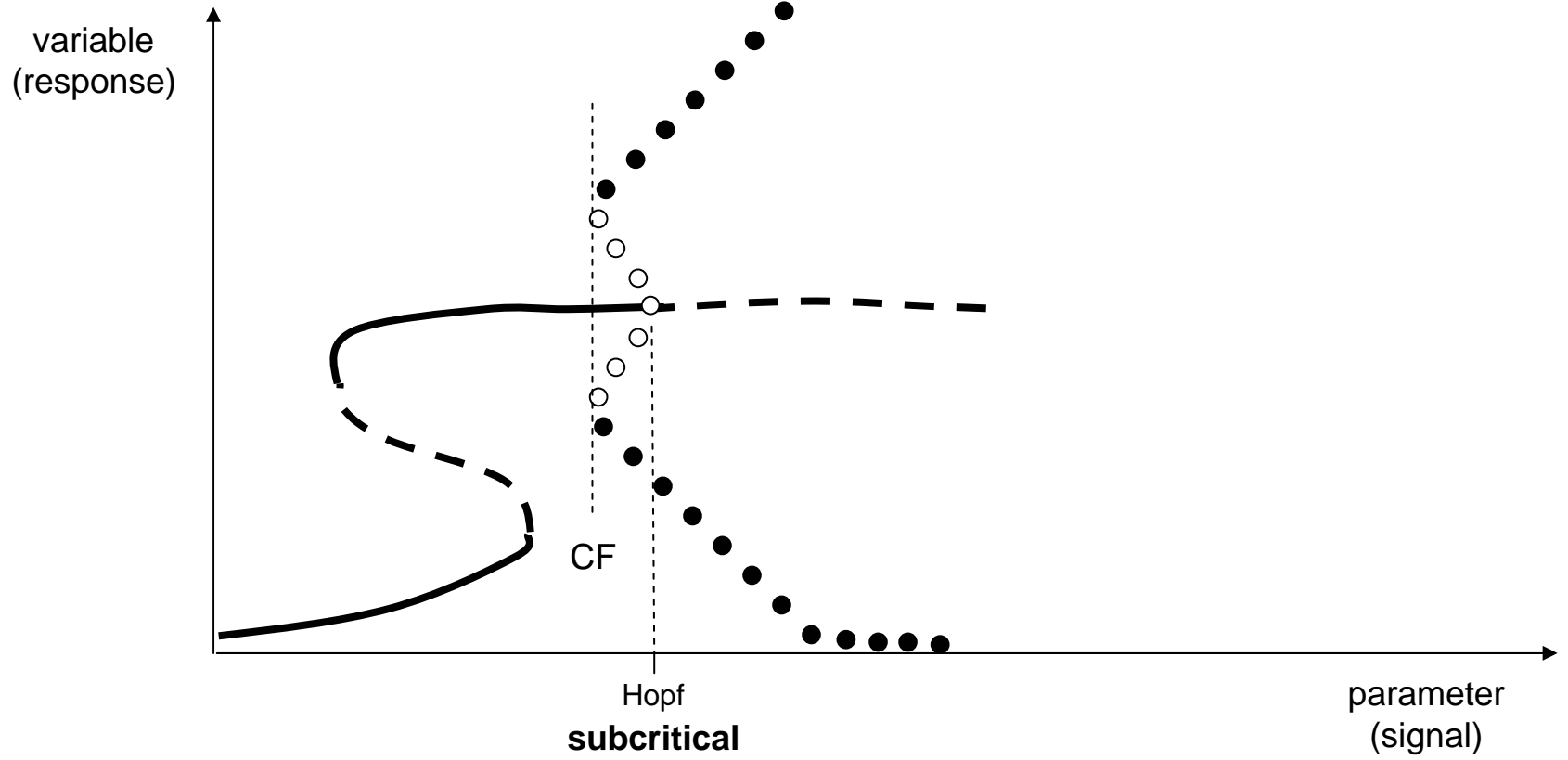


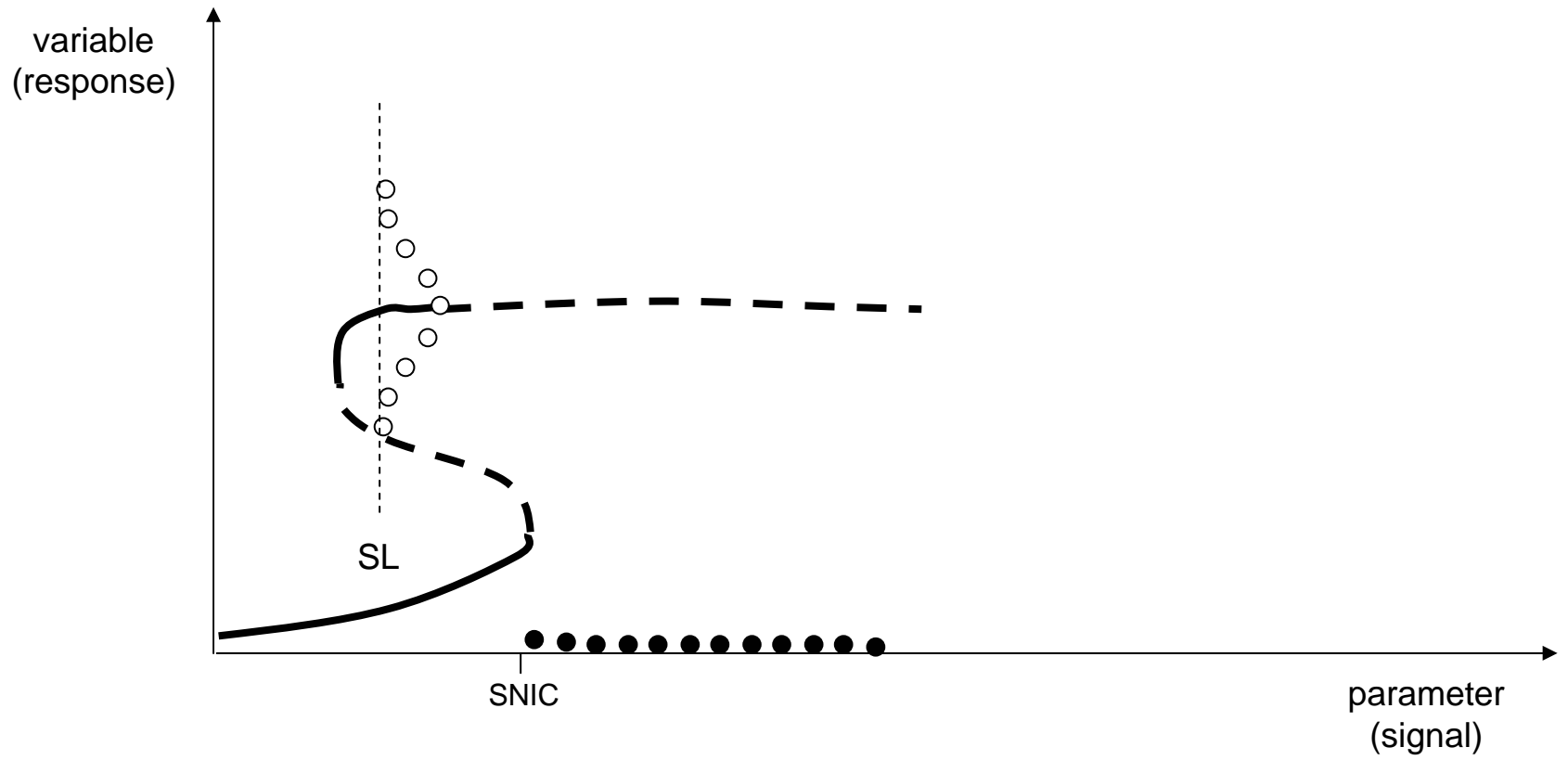


Hopf Bifurcation



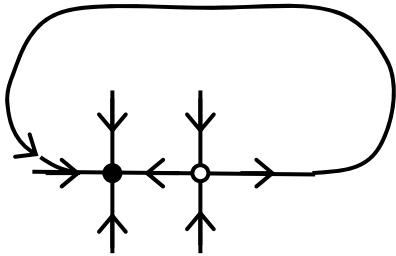




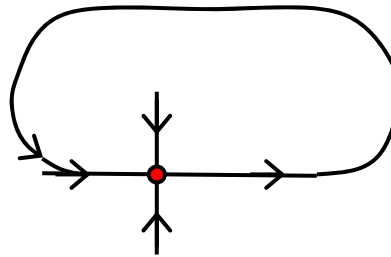


SNIC Bifurcation

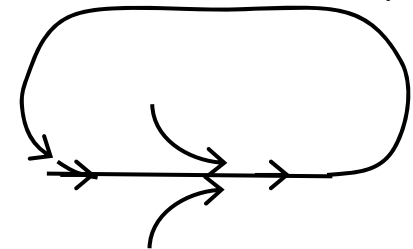
Invariant Circle



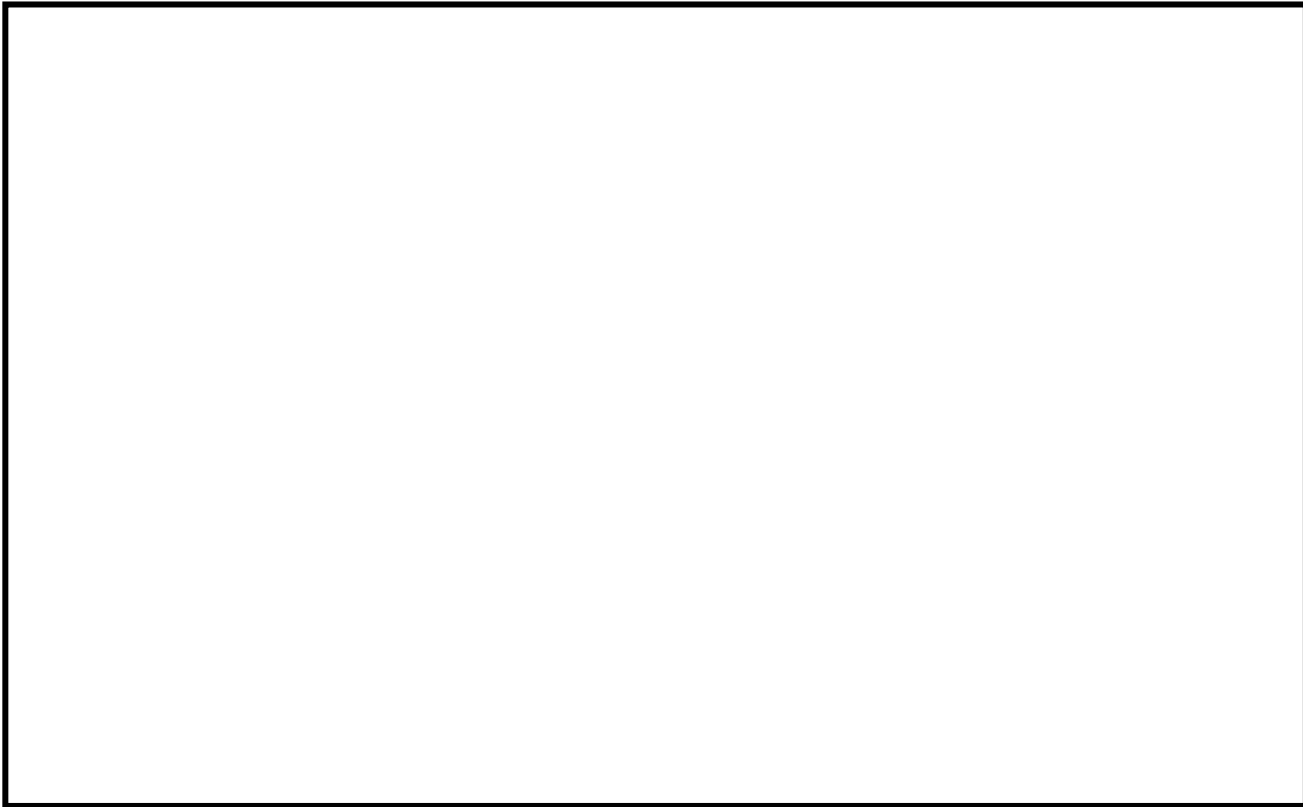
Saddle-Node on an Invariant Circle



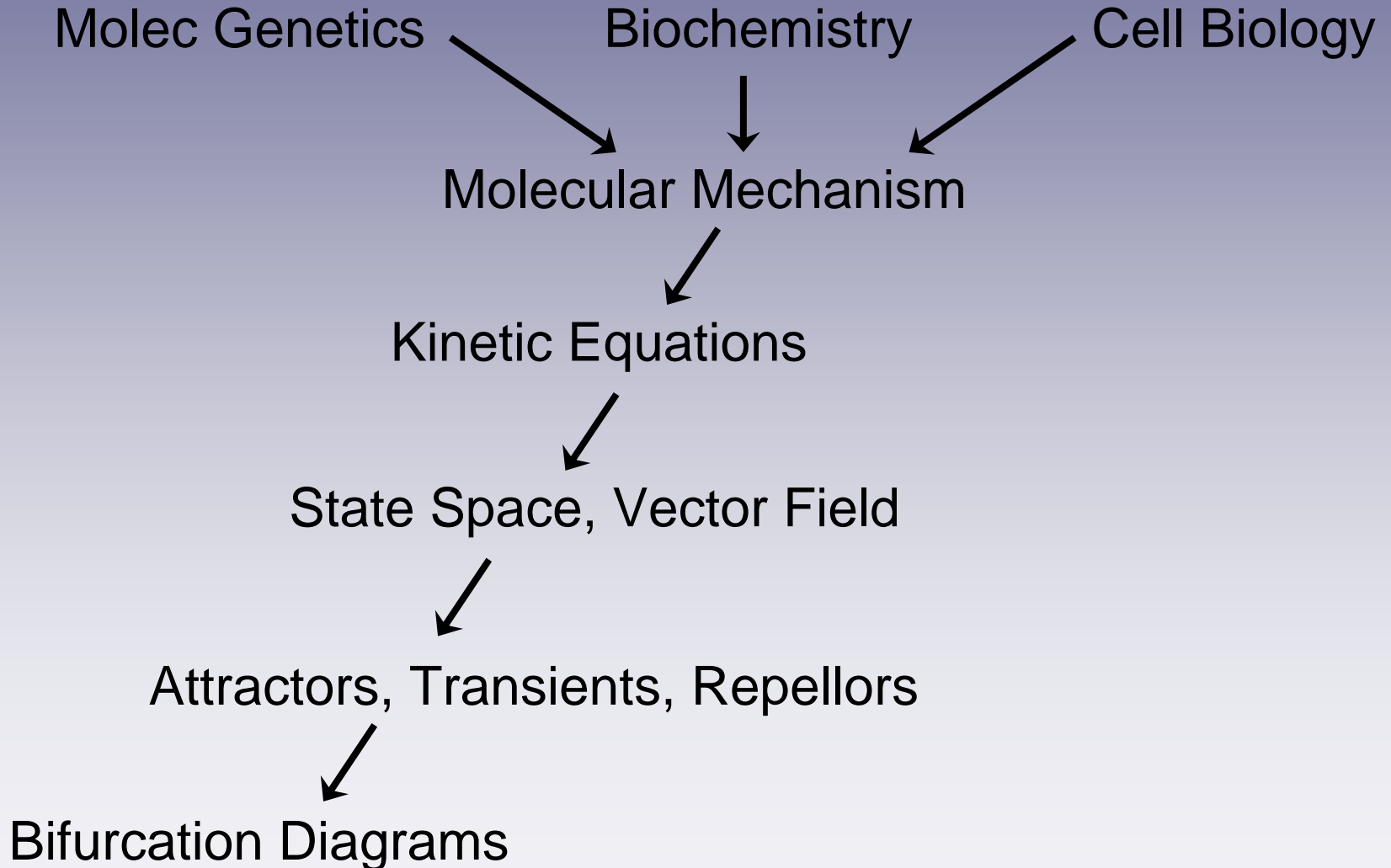
Limit Cycle



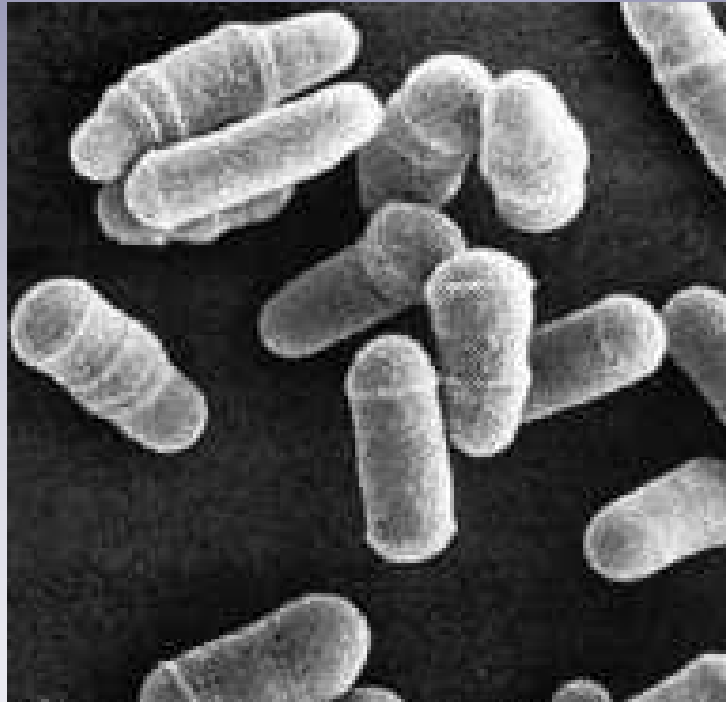
Signal-Response Curve =
One-parameter Bifurcation Diagram

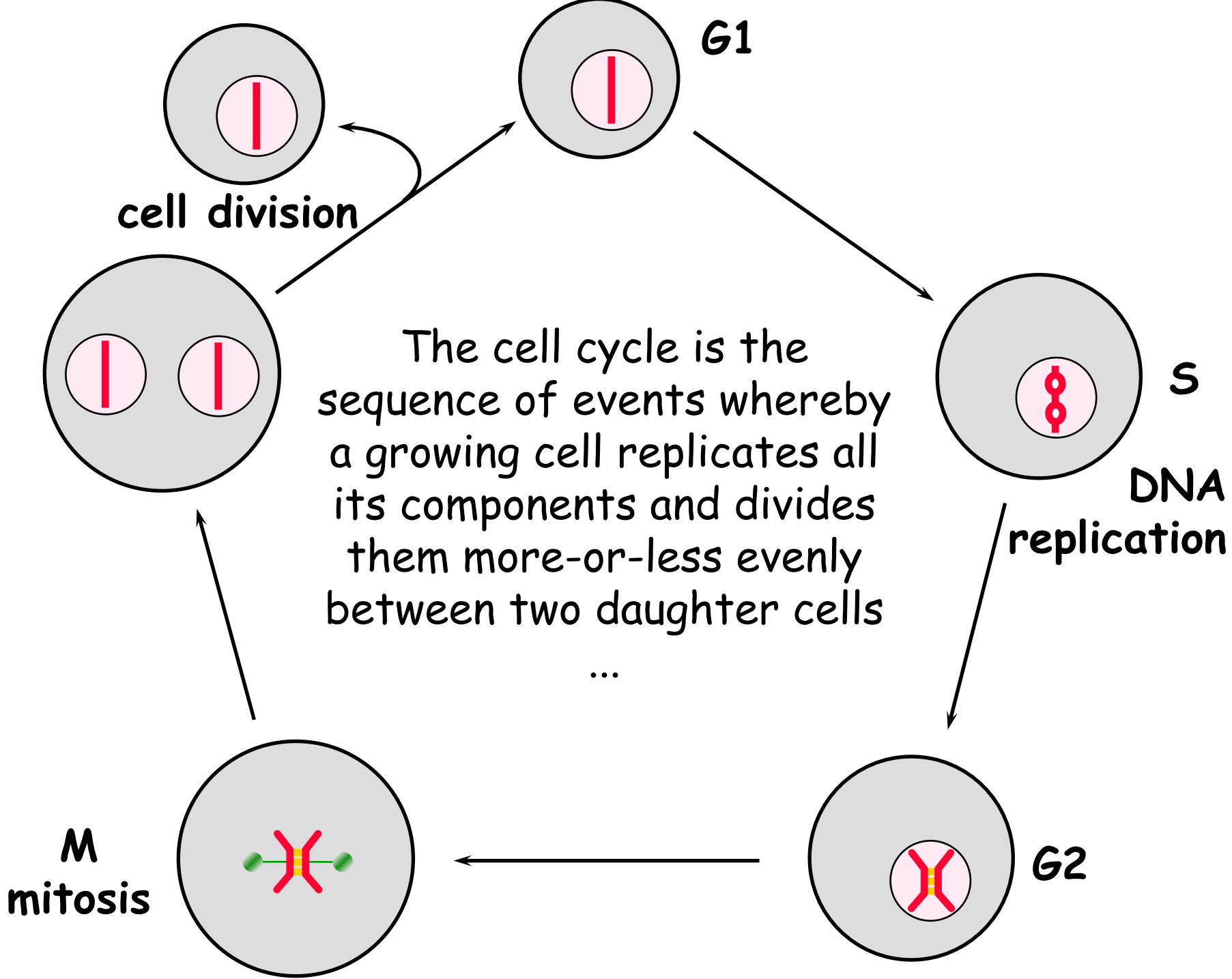


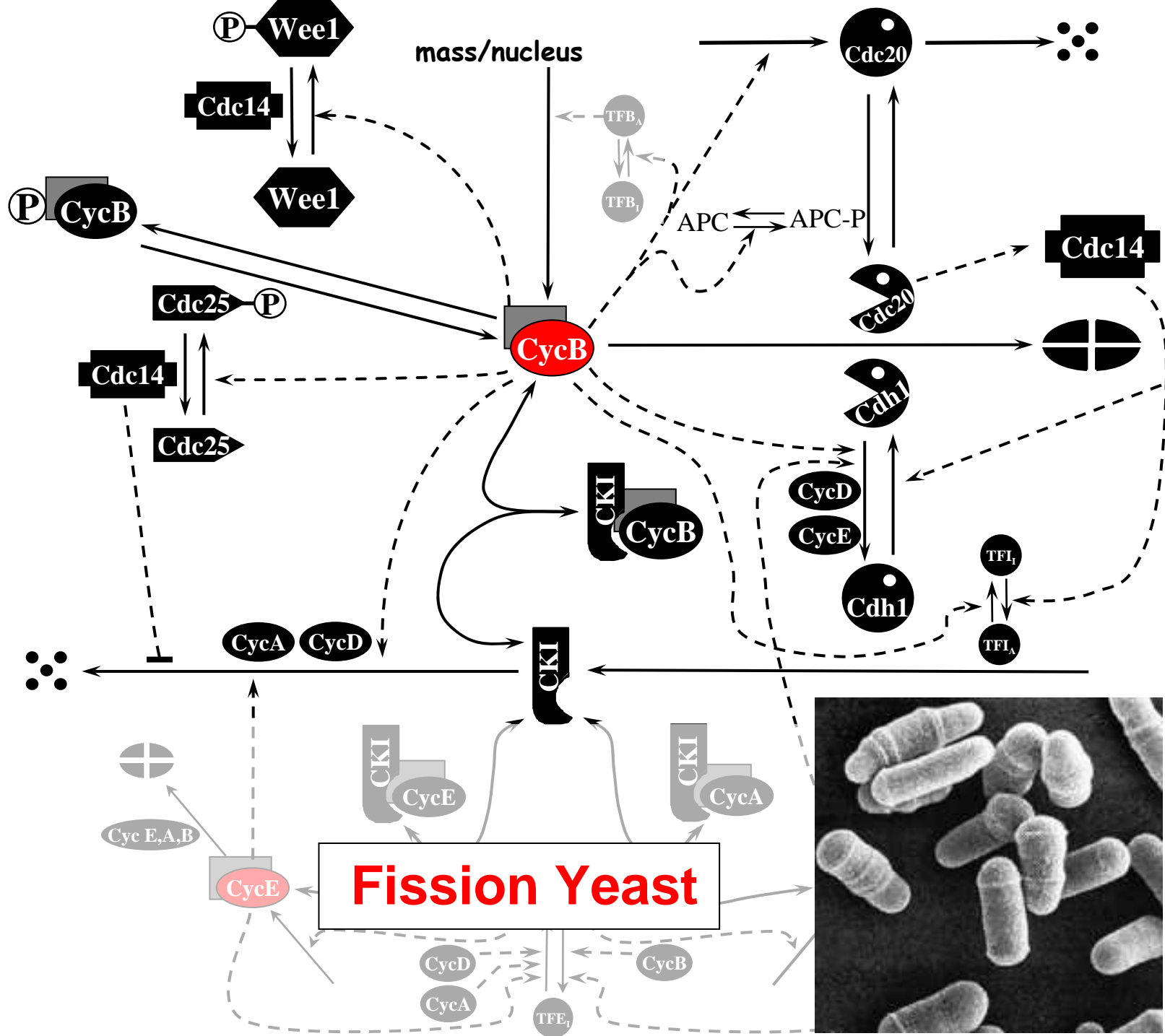
Review



The Cell Cycle of Fission Yeast





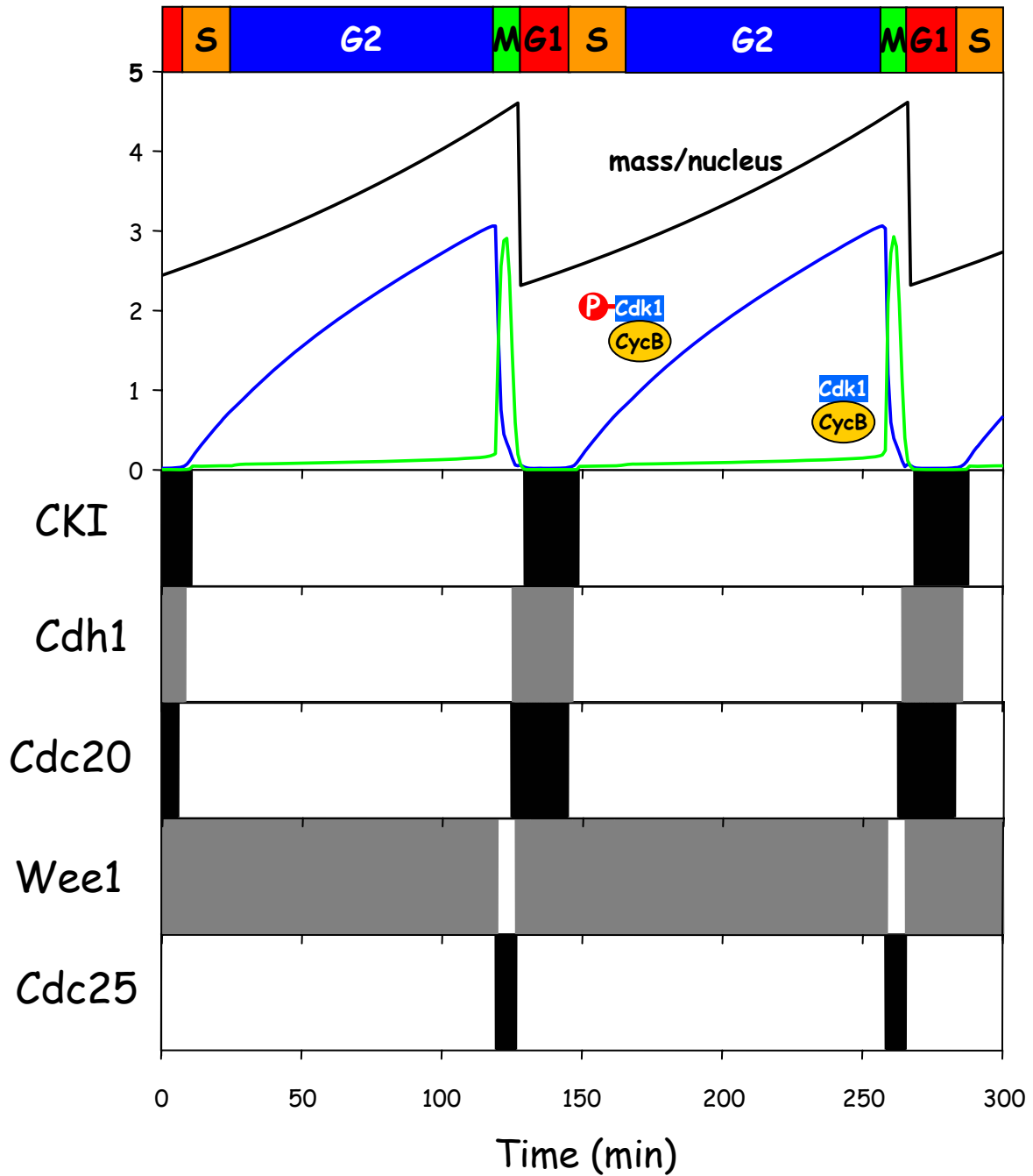


The mathematical model

$$\frac{d[\text{CycB}]}{dt} = \underbrace{k_3 [\text{mass}]}_{\text{synthesis}} - \underbrace{\left(k_4 + k_4'[\text{Cdh1}] + k_4''[\text{Cdc20}]\right)[\text{CycB}]}_{\text{degradation}} - \underbrace{k_5[\text{CKI}][\text{CycB}]}_{\text{binding}}$$

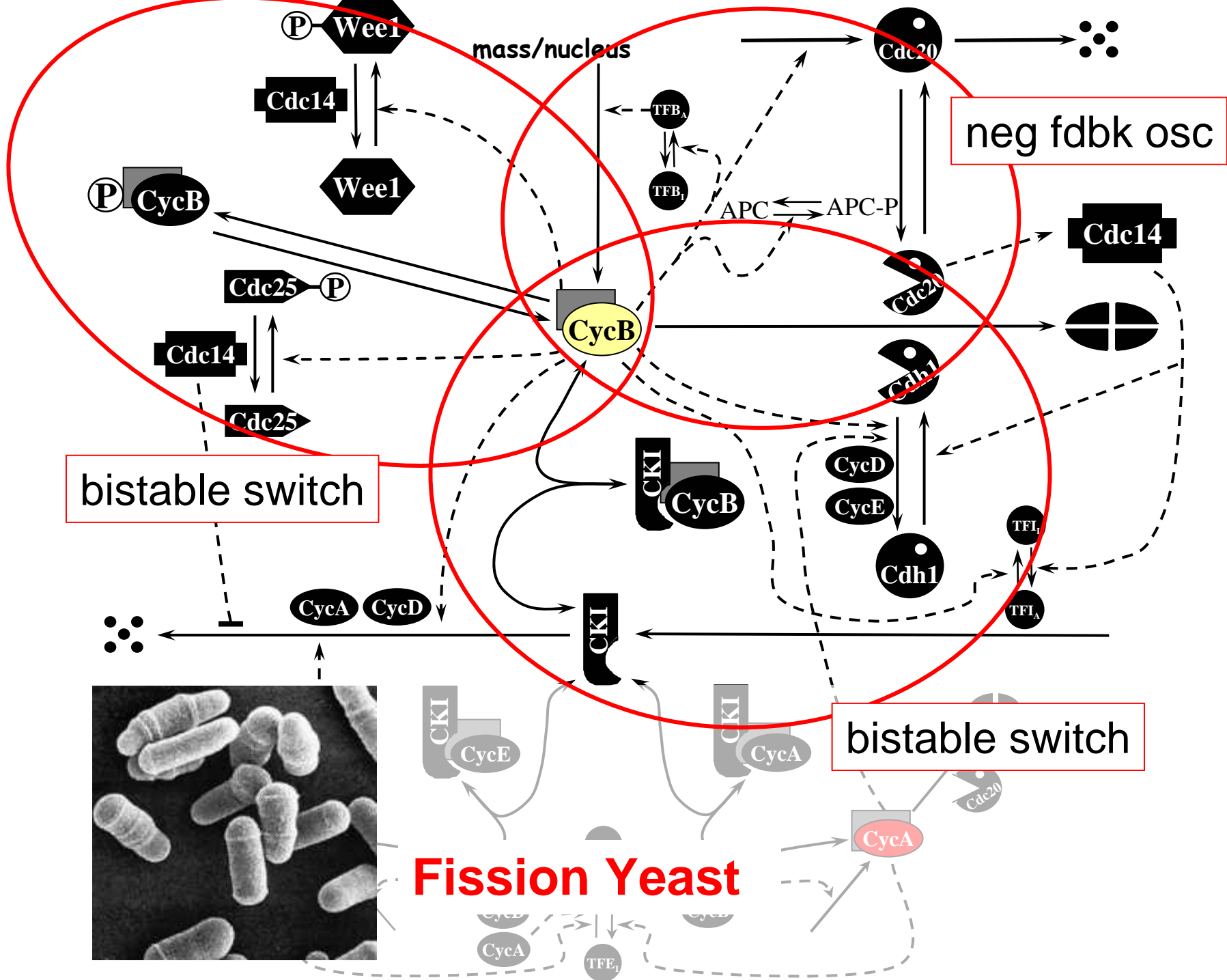
$$\frac{d[\text{Cdh1}]}{dt} = \underbrace{\frac{\left(k_6 + k_6'[\text{Cdc14}]\right)\left([\text{Cdh1}]_T - [\text{Cdh1}]\right)}{J_6 + [\text{Cdh1}]_T - [\text{Cdh1}]}}_{\text{activation}} - \underbrace{\frac{\left(k_7 + k_7'[\text{CycB}]\right)[\text{Cdh1}]}{J_7 + [\text{Cdh1}]}}_{\text{inactivation}}$$

$$\frac{d[\text{Cdc20}]}{dt} = \underbrace{k_1 + \frac{k_1'[\text{CycB}]^n}{J_1^n + [\text{CycB}]^n}}_{\text{synthesis}} - \underbrace{k_2[\text{Cdc20}]}_{\text{degradation}}$$



Mutants in Fission Yeast

<u>Gene</u>	<u>Viable?</u>	<u>Trait</u>
<i>cdc2</i> ⁻	No	block in G2
<i>cdc13</i> ⁻	No	block in G2
<i>rum1</i> ⁻	Yes	sterile
<i>ste9</i> ⁻	Yes	sterile
<i>slp1</i> ⁻	Yes	
<i>wee1</i> ⁻	Yes	small
<i>cdc25</i> ⁻	No	block in G2
<i>cdc2</i> ^{OP}	Yes	wt
<i>cdc13</i> ^{OP}	Yes	wt
<i>rum1</i> ^{OP}	No	endoreplic.
<i>ste9</i> ^{OP}	Yes	wt
<i>wee1</i> ^{OP}	Yes	large
<i>cdc25</i> ^{OP}	Yes	small
<i>wee1</i> ⁻ <i>rum1</i> Δ	No	extremely small
<i>wee1</i> ⁻ <i>cdc25</i> Δ	Yes	quantized cycles
<i>wee1</i> ⁻ <i>cdc25</i> ^{OP}	No	cut
<i>wee1</i> ^{OP} <i>cdc25</i> ⁻	No	block in G2



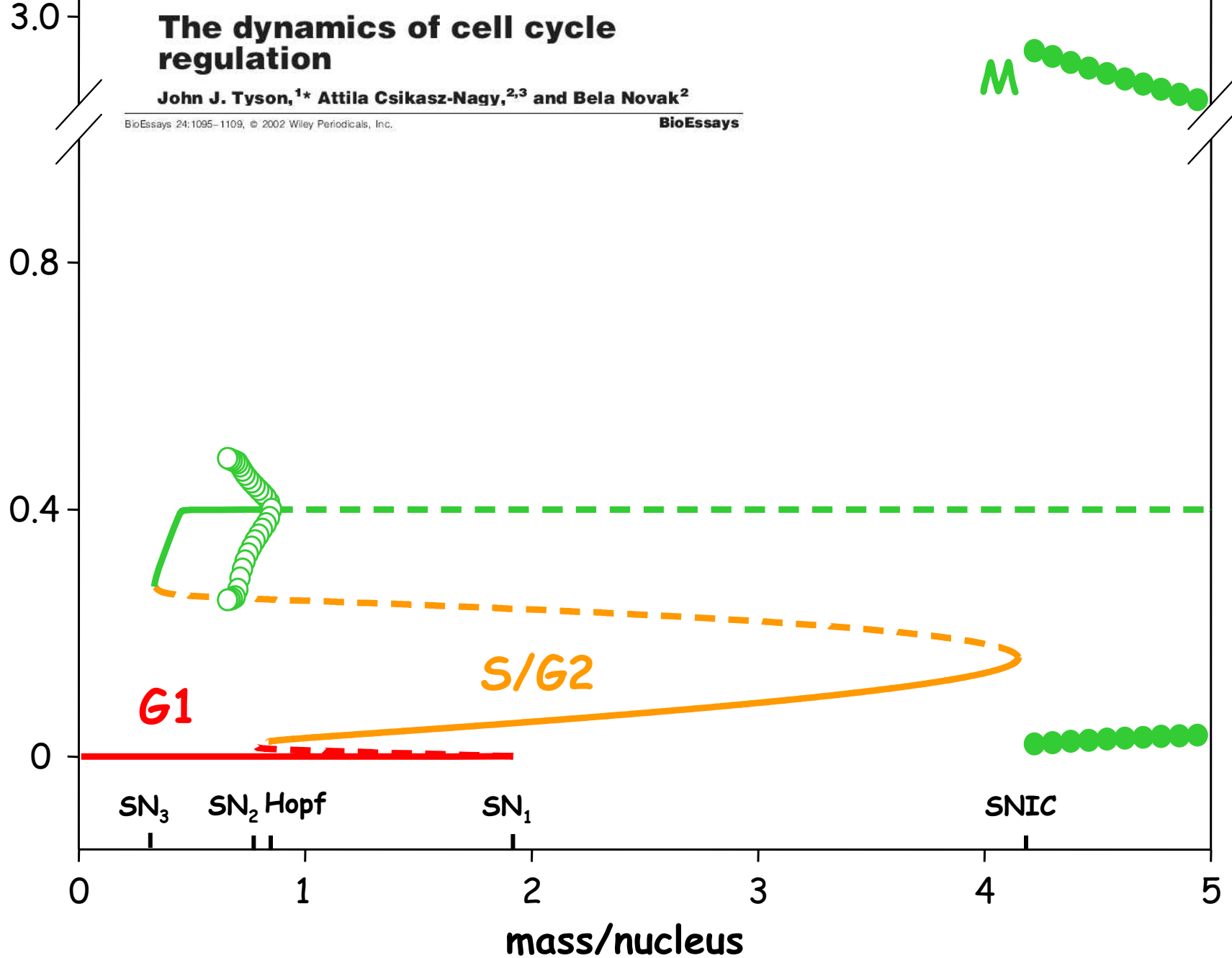
The dynamics of cell cycle regulation

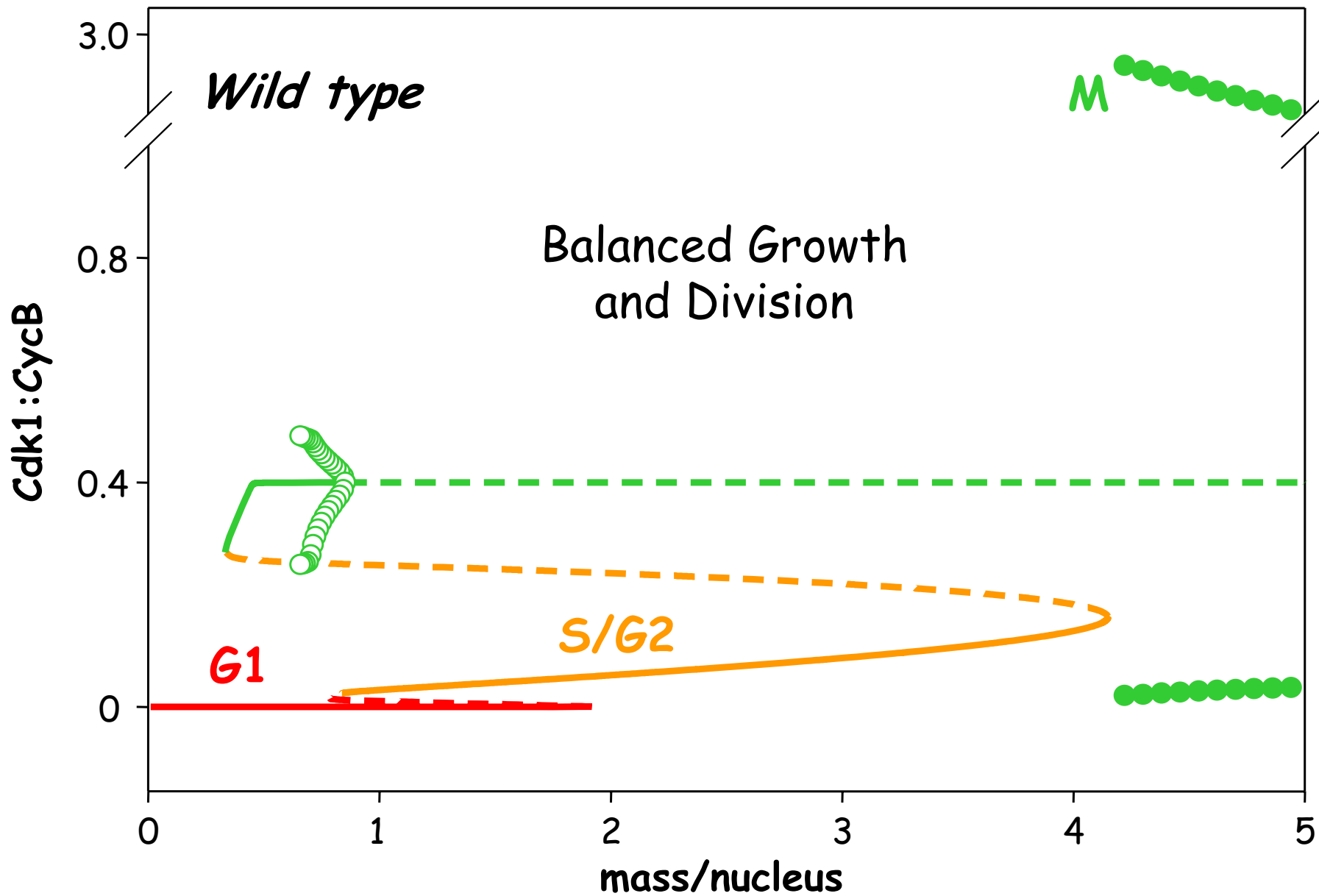
John J. Tyson,^{1*} Attila Csikasz-Nagy,^{2,3} and Bela Novak²

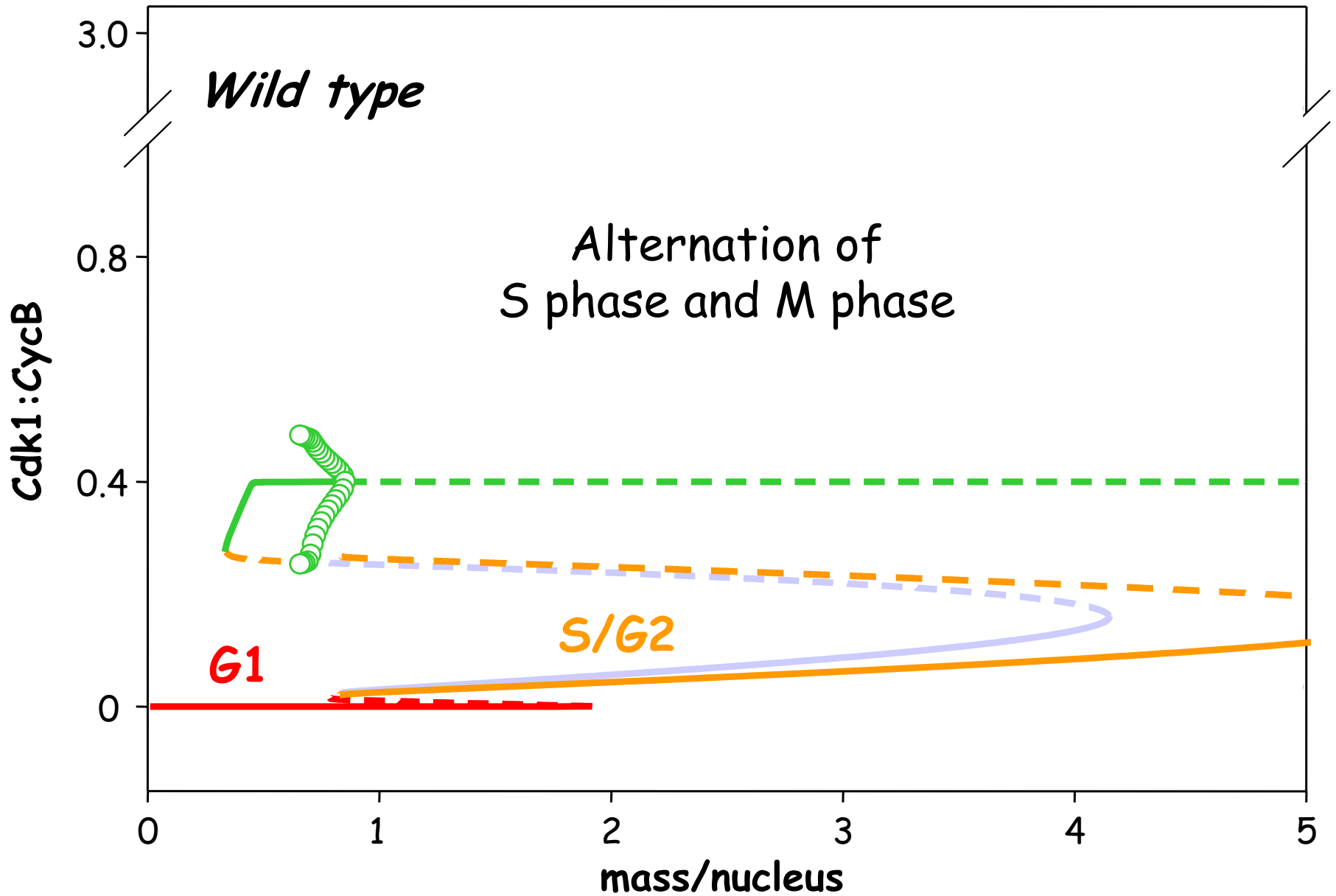
BioEssays 24:1095–1109, © 2002 Wiley Periodicals, Inc.

BioEssays

Cdk1:CycB



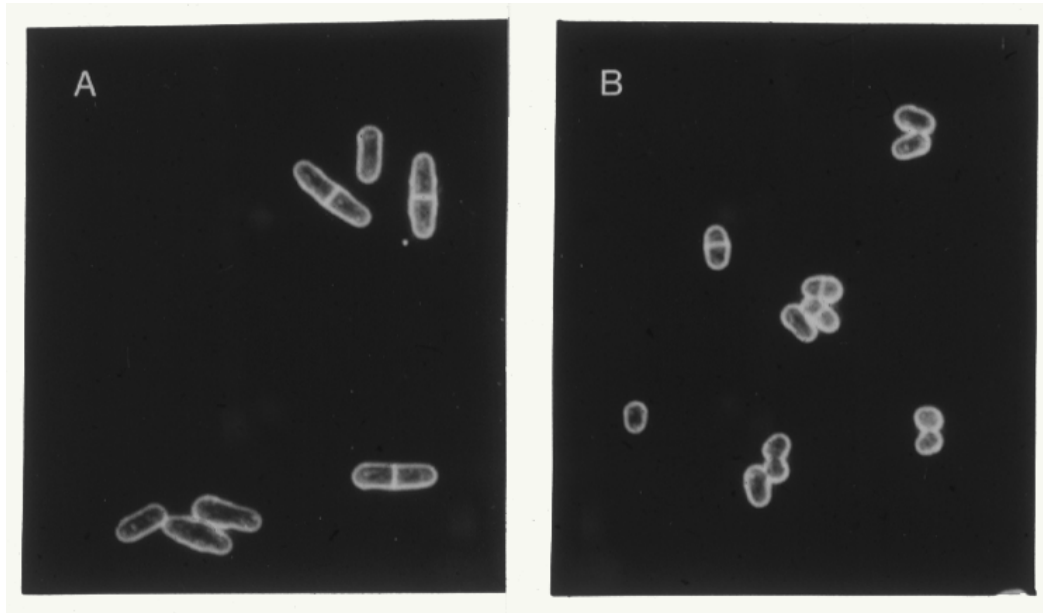




Genetic control of cell size at cell division in yeast

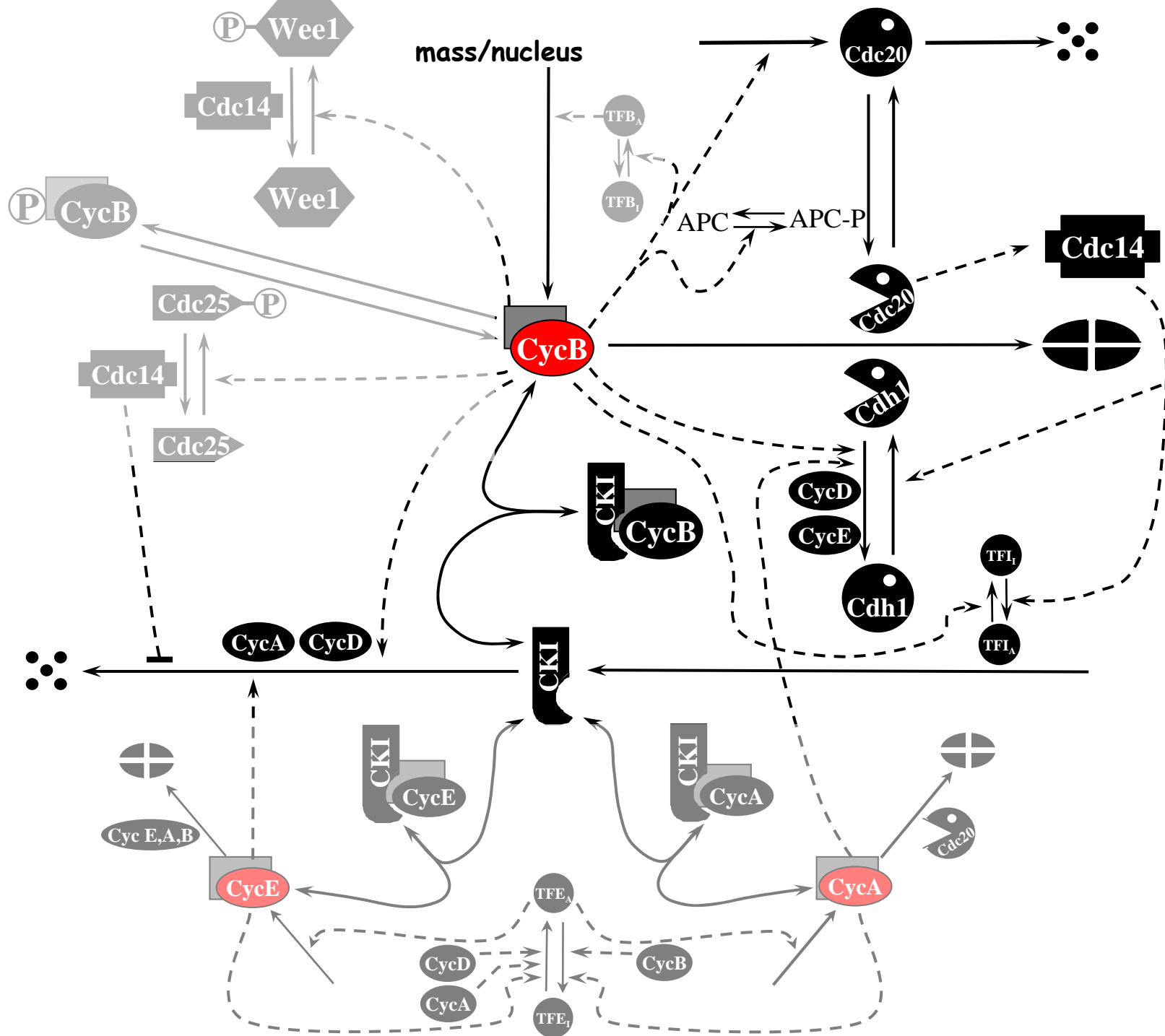
Paul Nurse

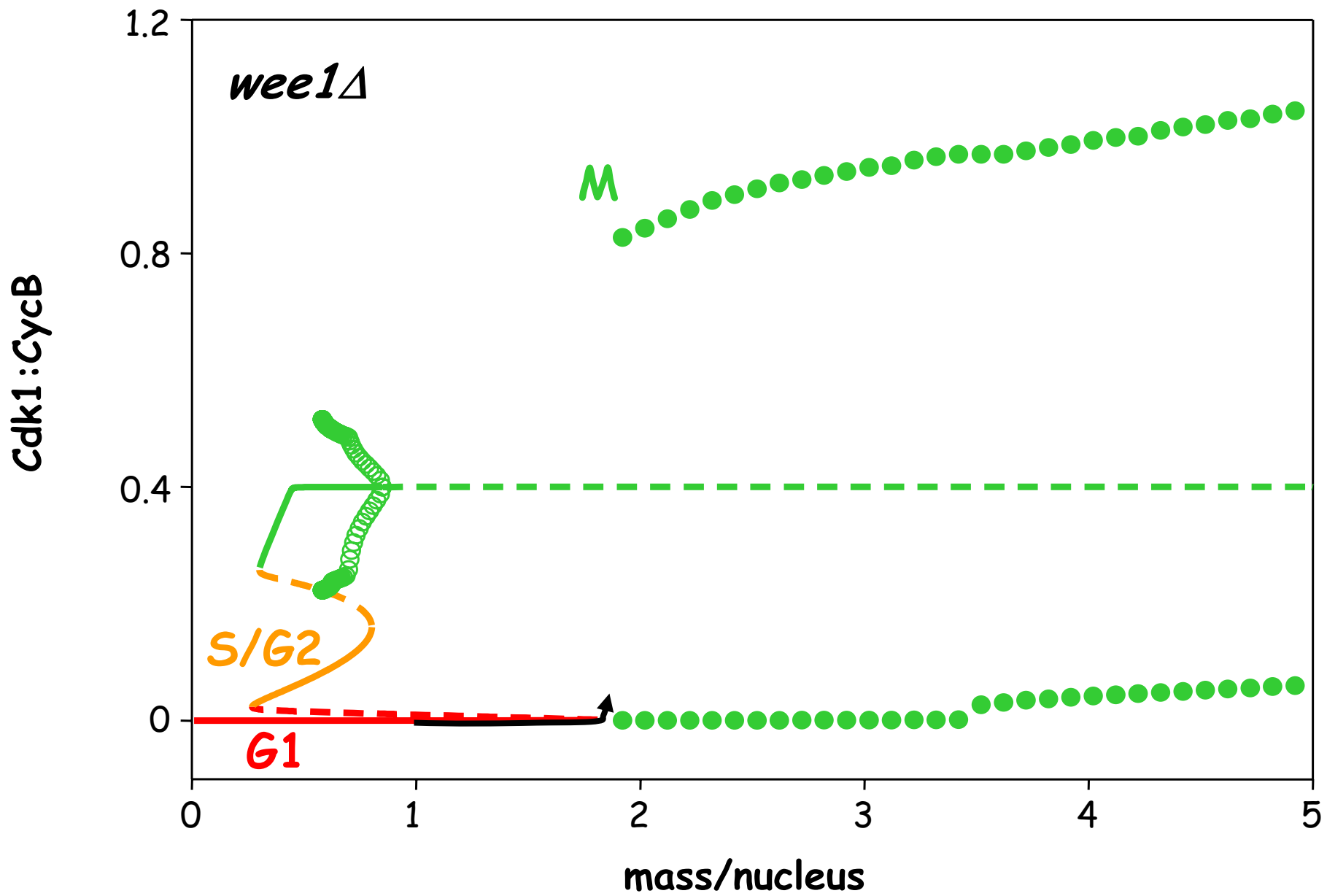
Department of Zoology, West Mains Road, Edinburgh EH9 3JT, UK

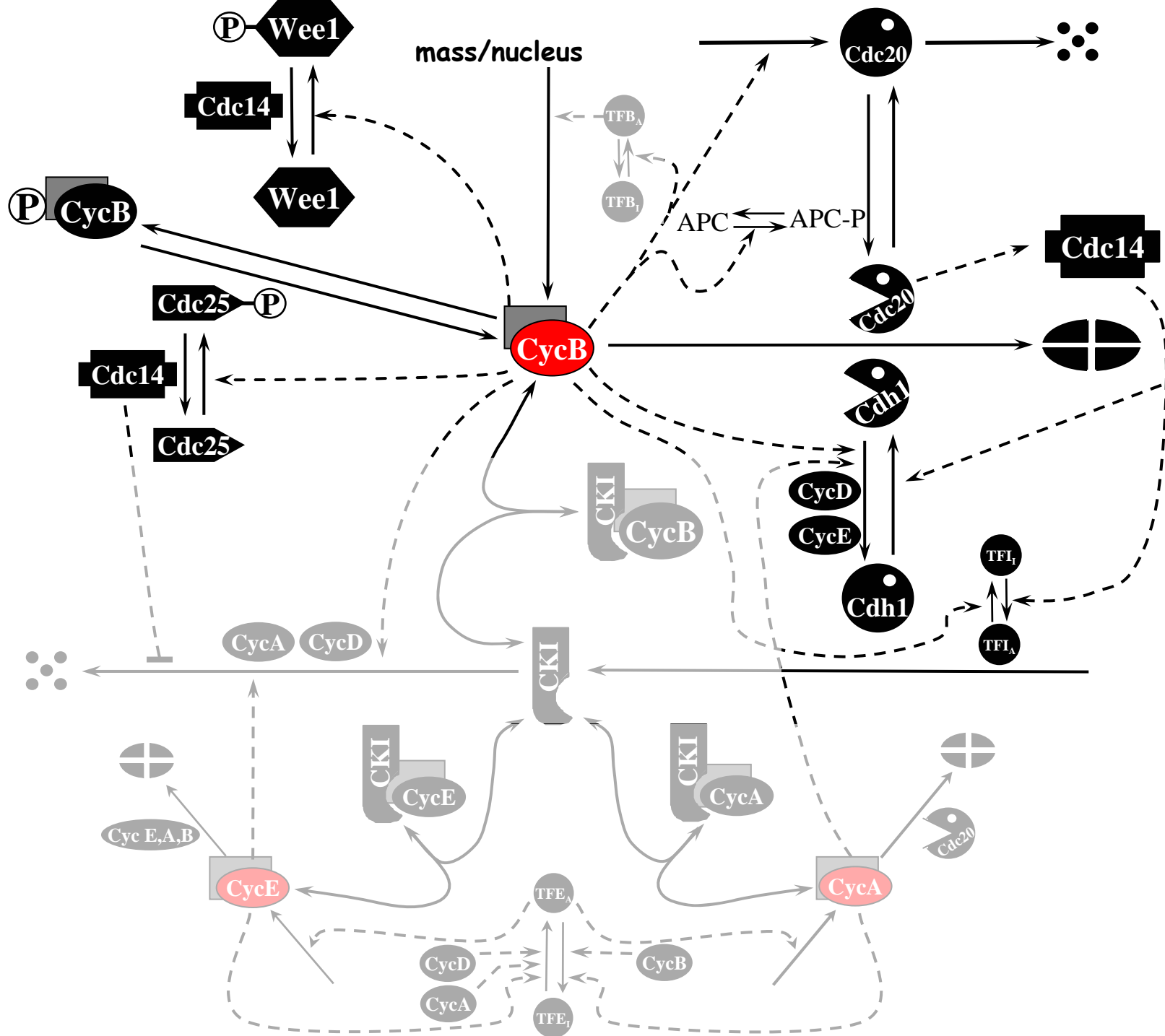


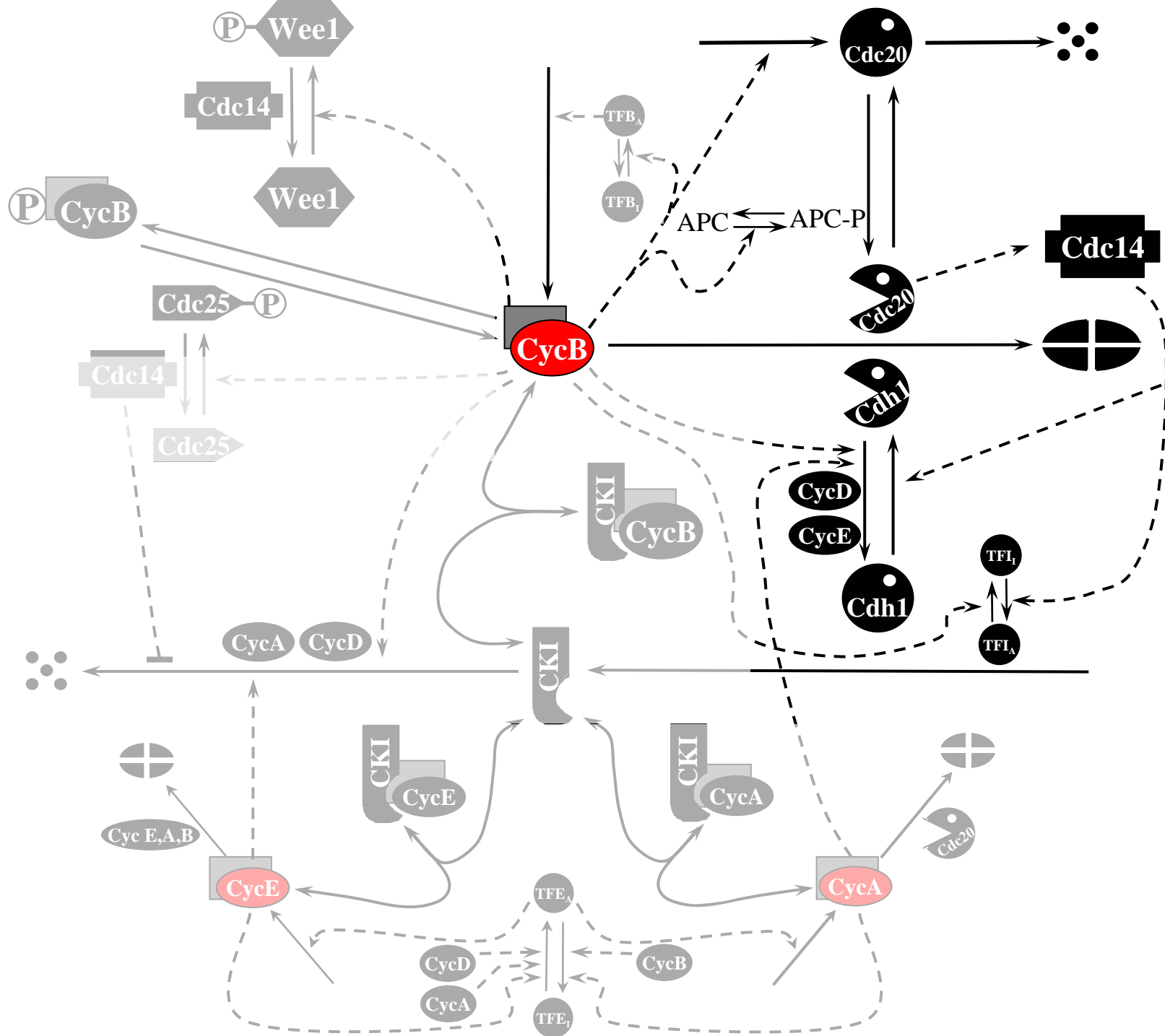
wild-type

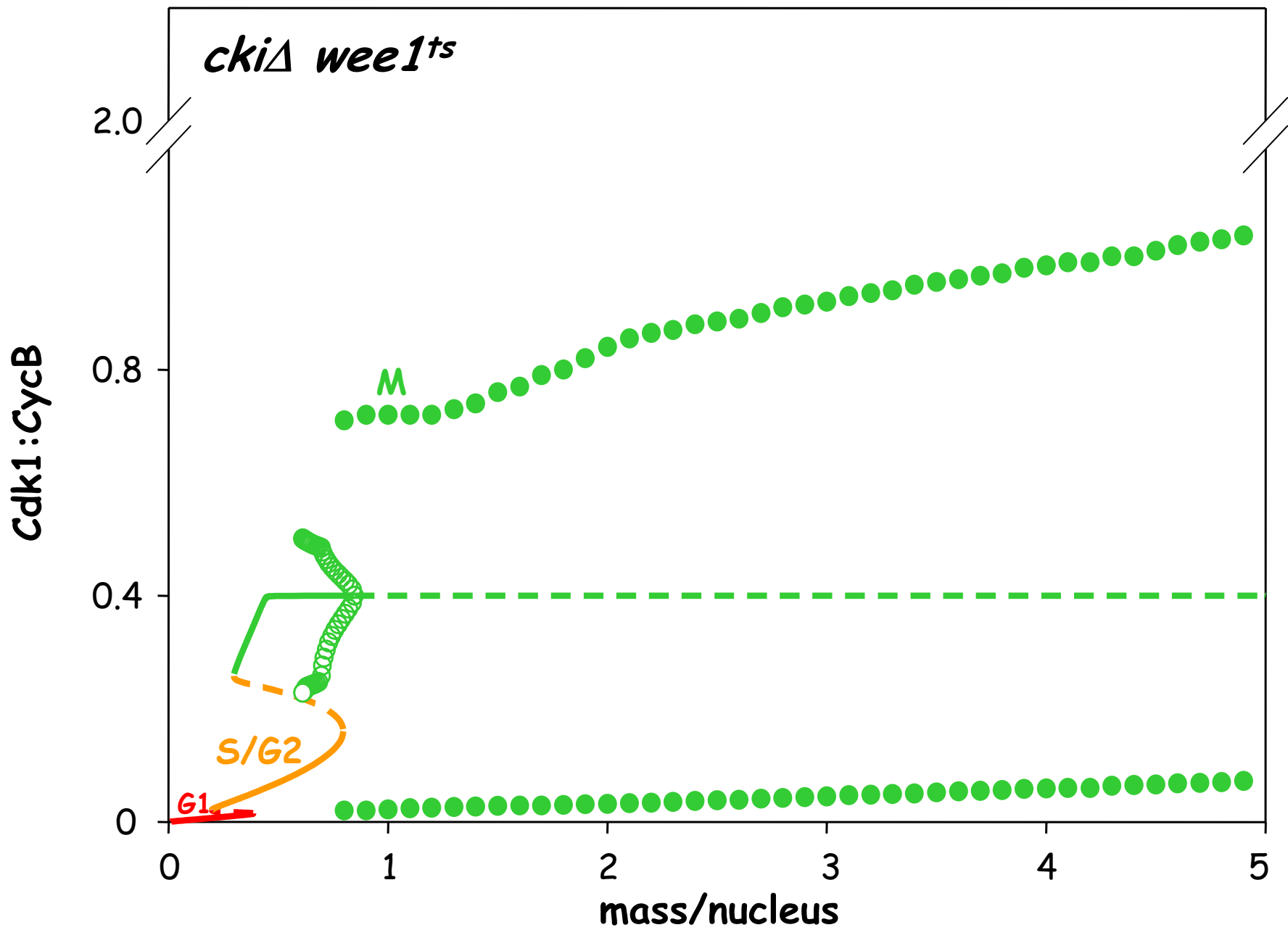
***wee1*Δ**



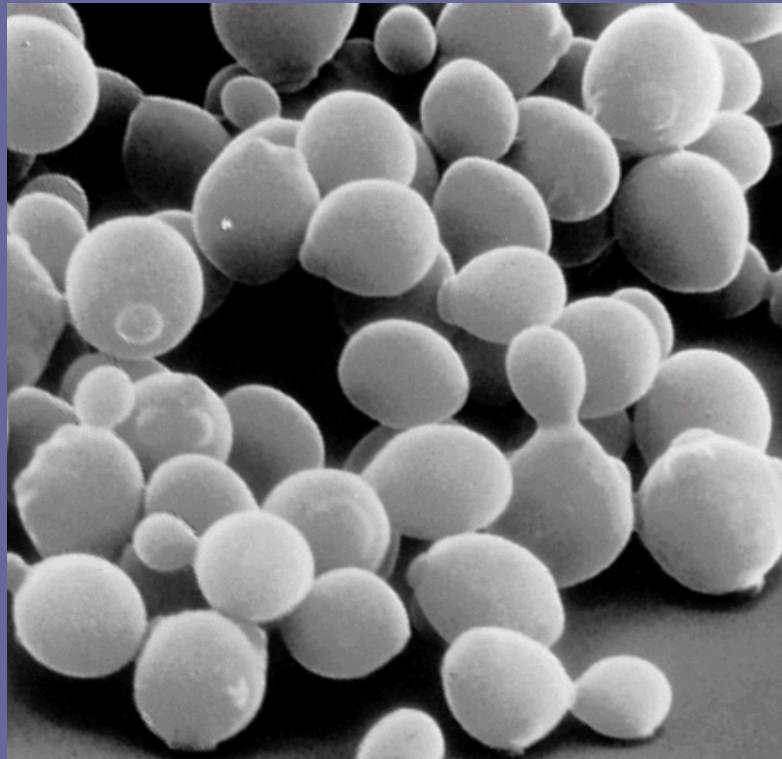


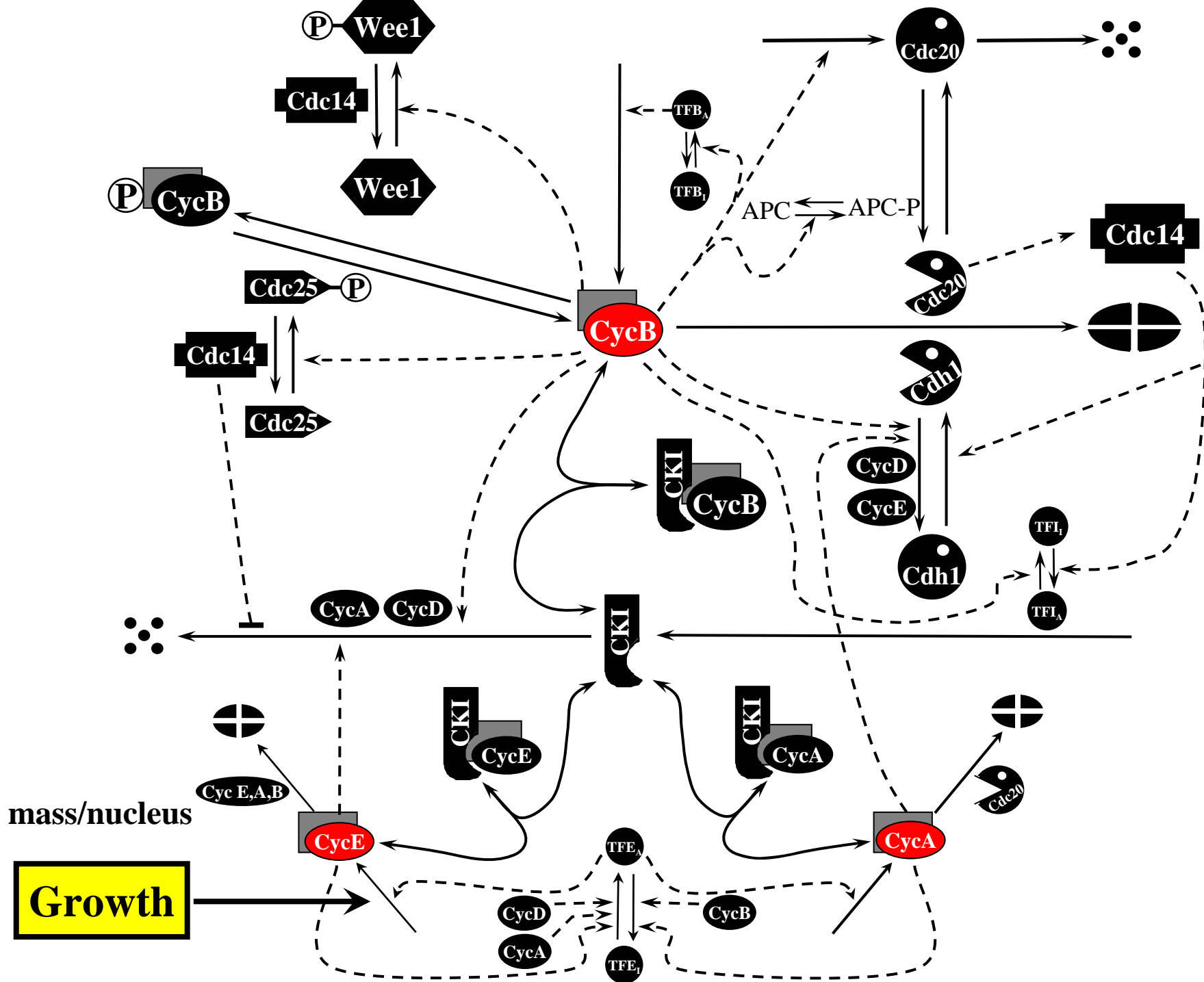




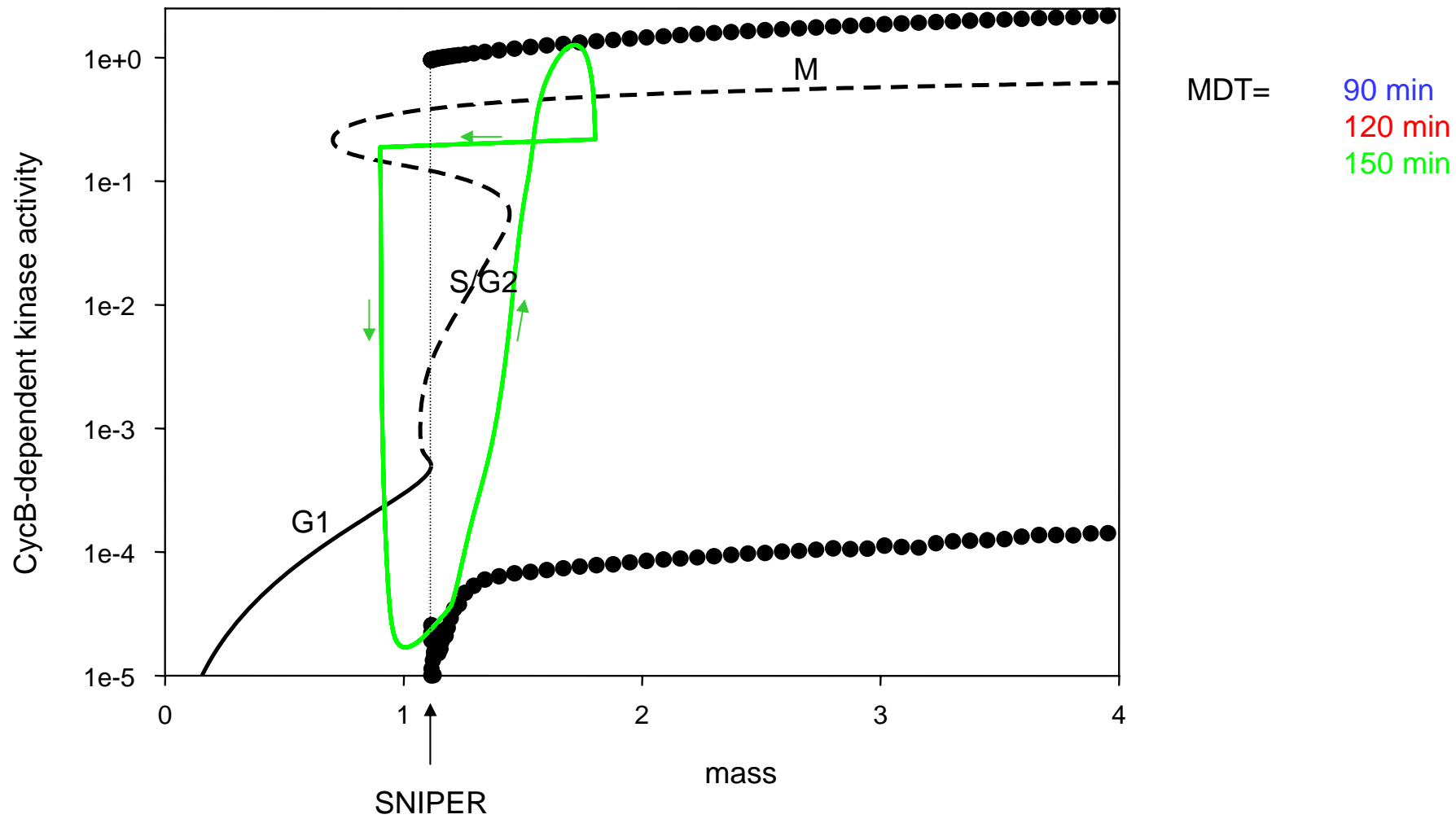


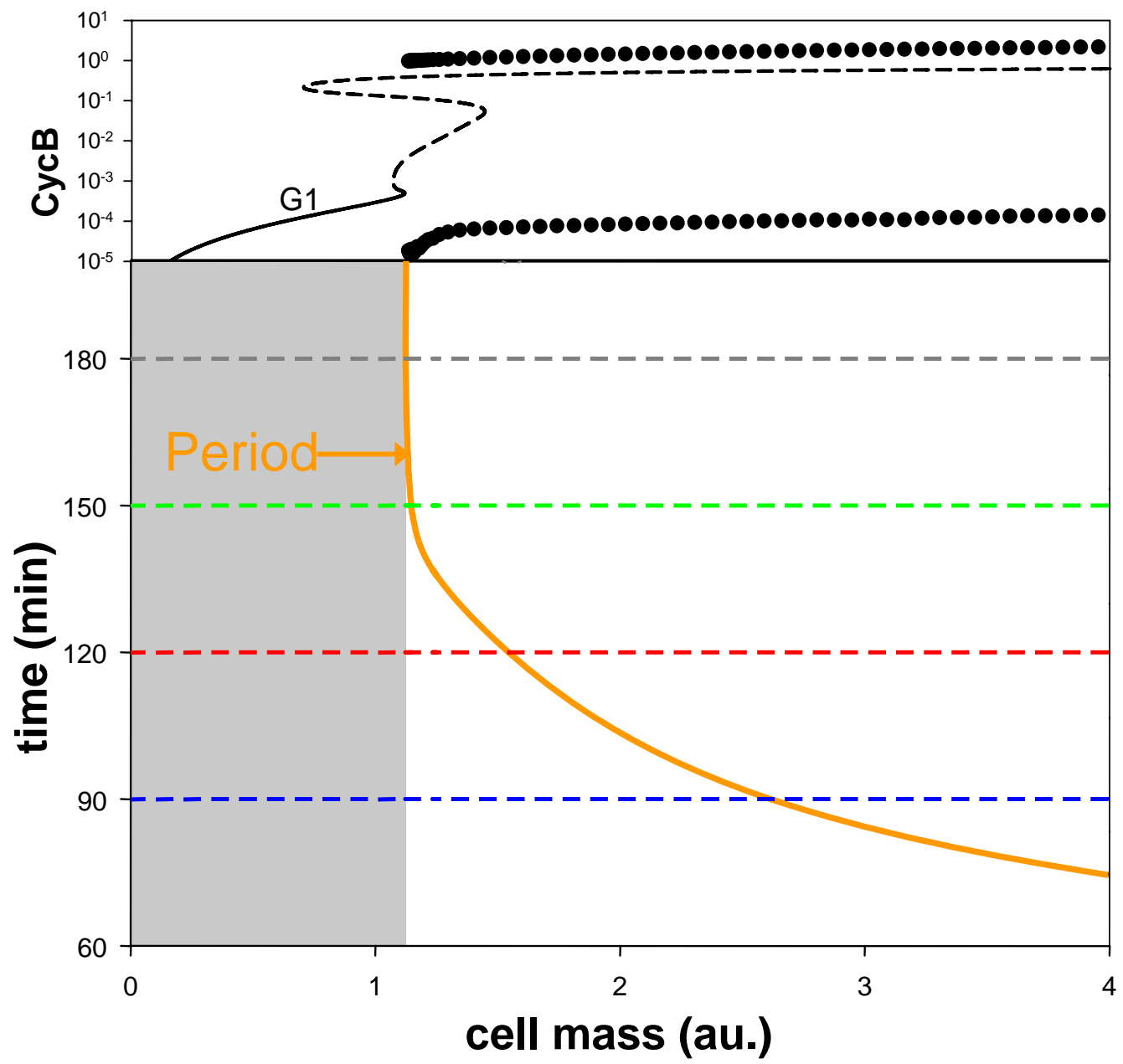
The Cell Cycle of Budding Yeast



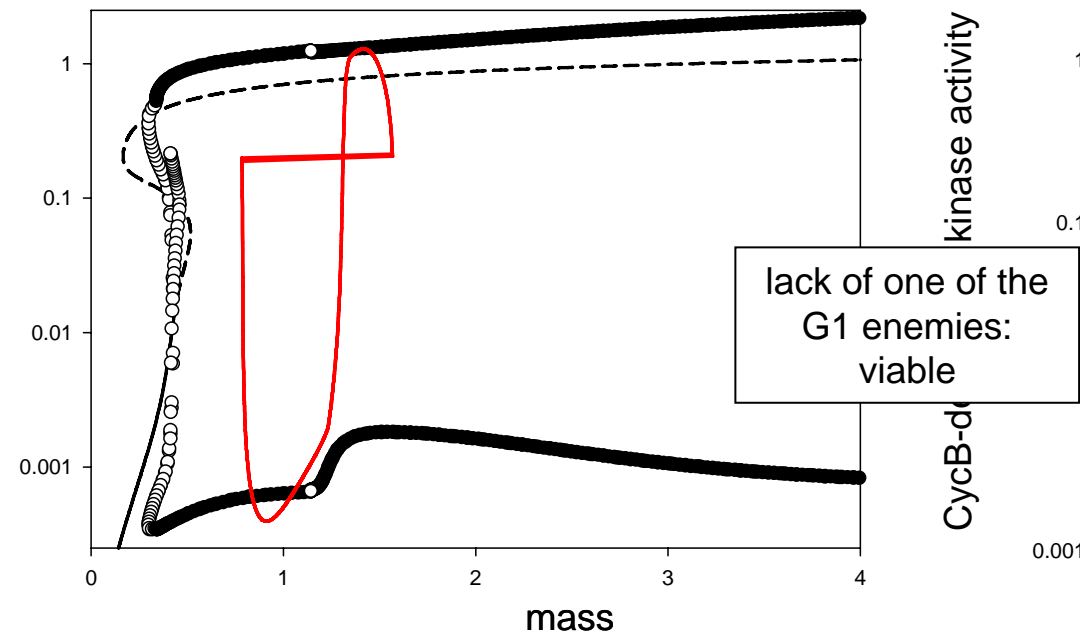


Wild type cells

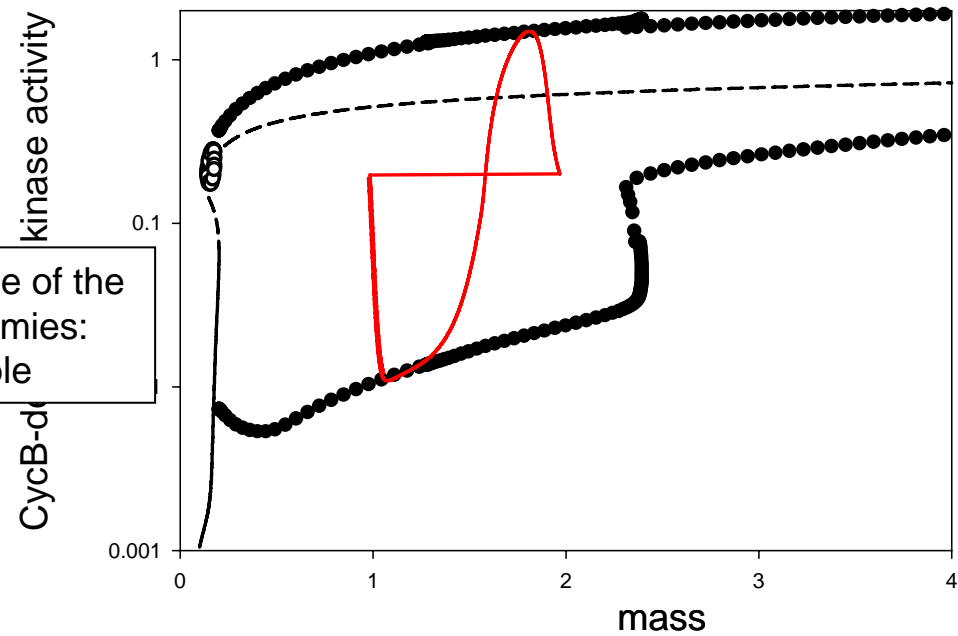




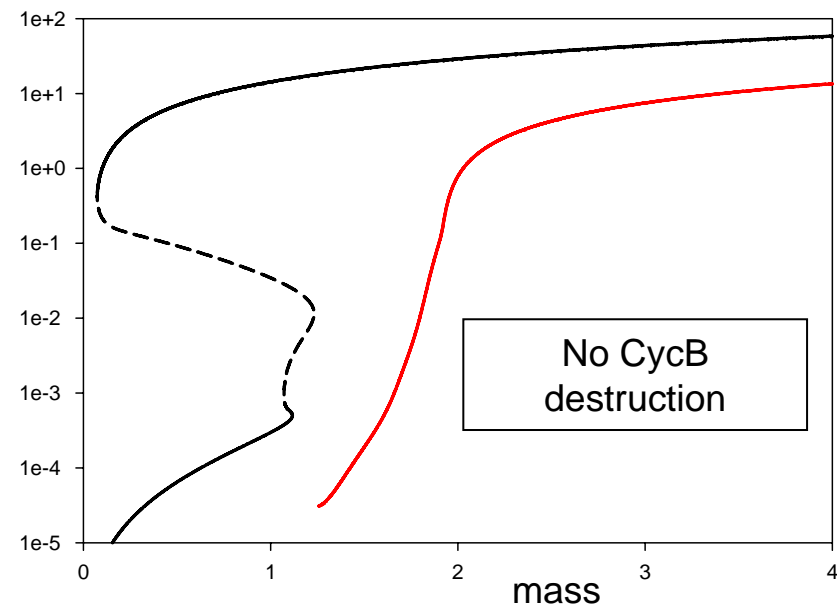
cdh1 Δ



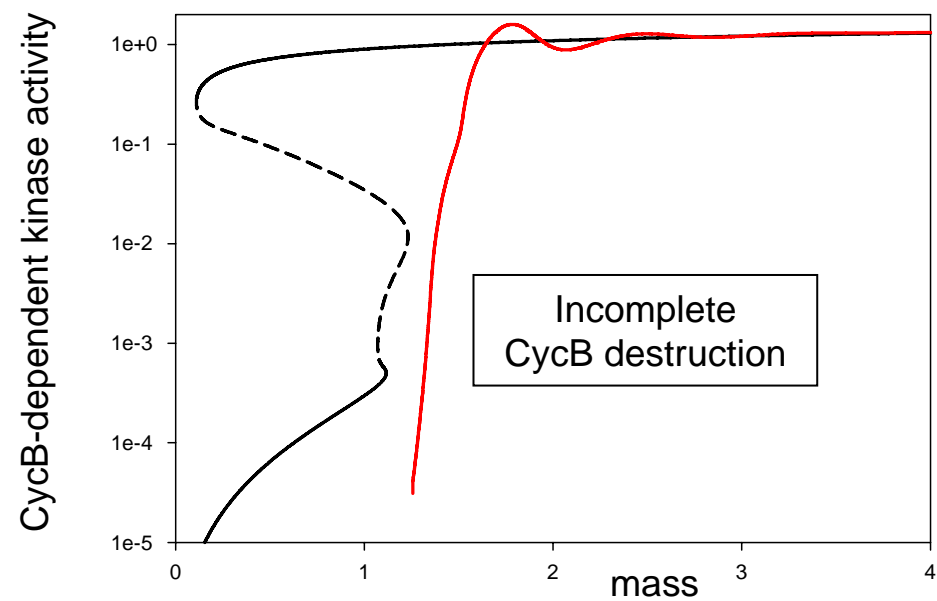
cki Δ



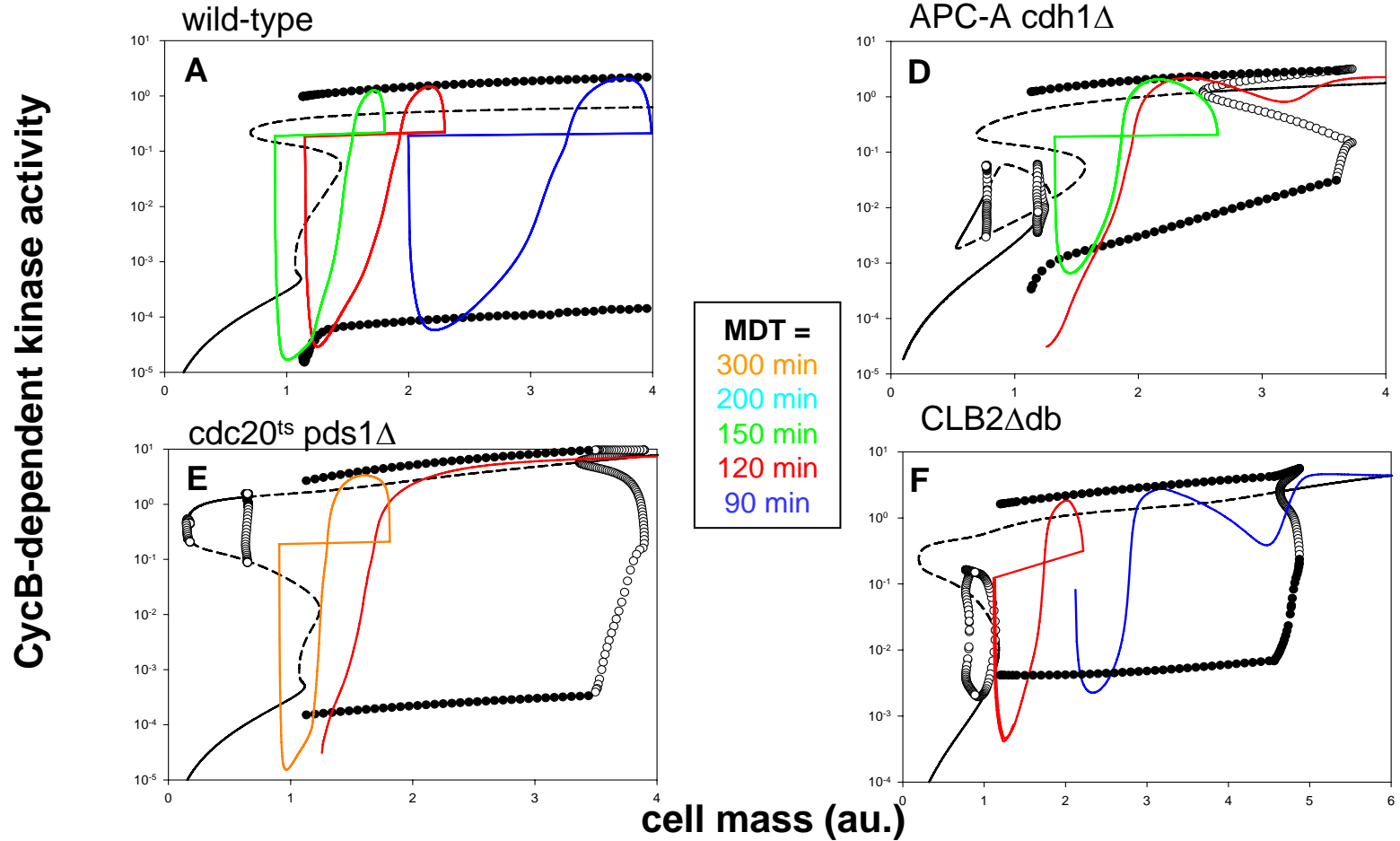
cdc20 Δ



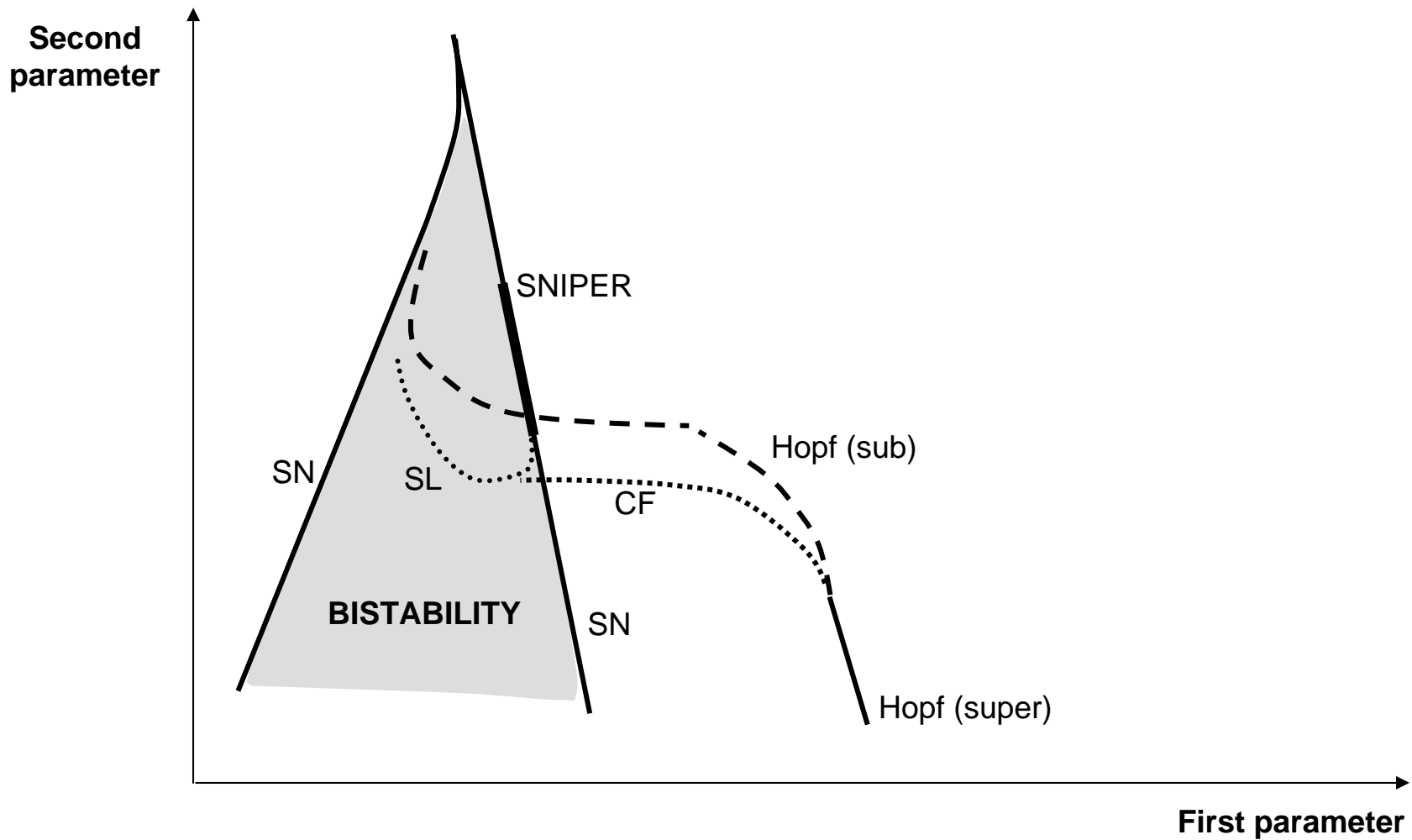
cdc14 Δ



Defects in Exit from Mitosis

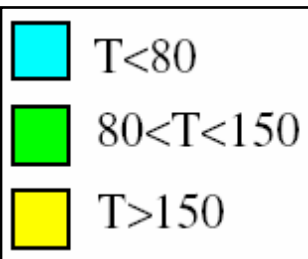
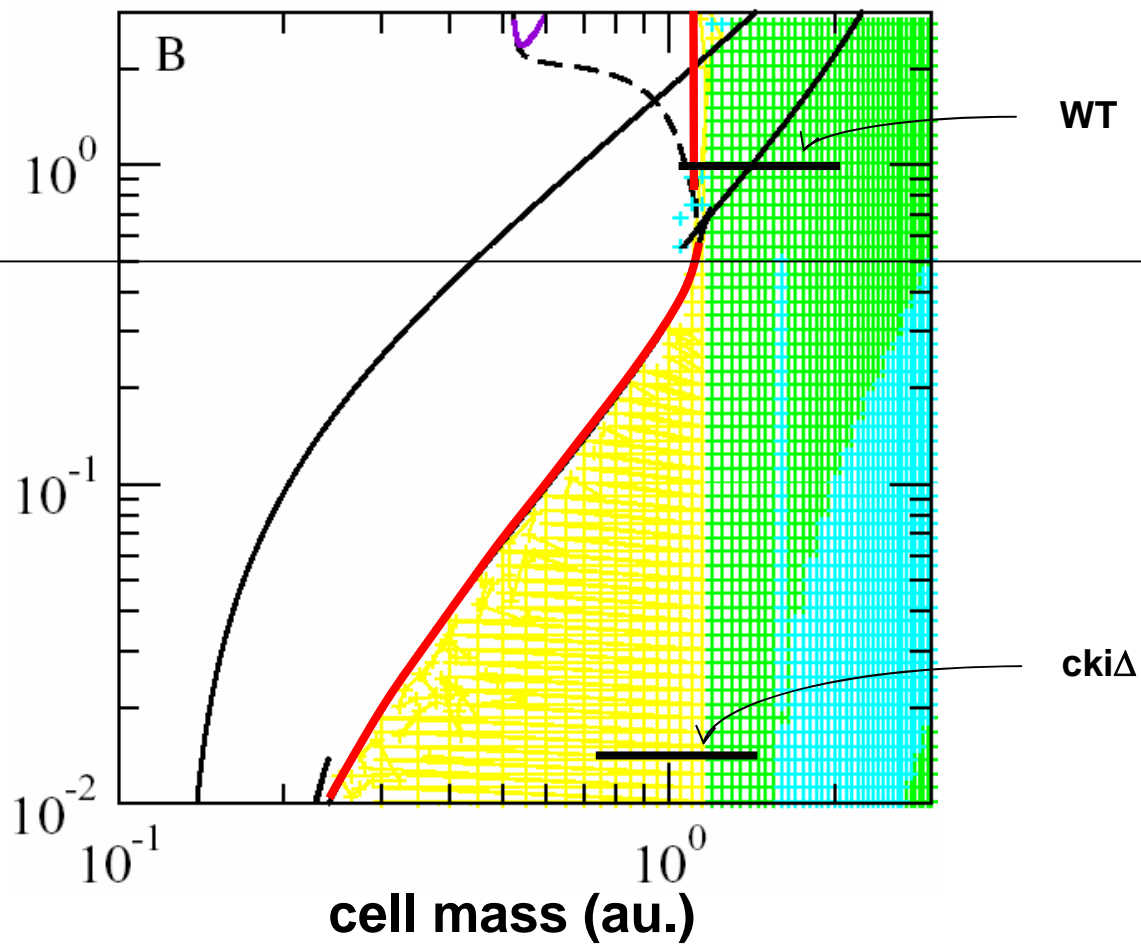


Two-parameter bifurcation diagram

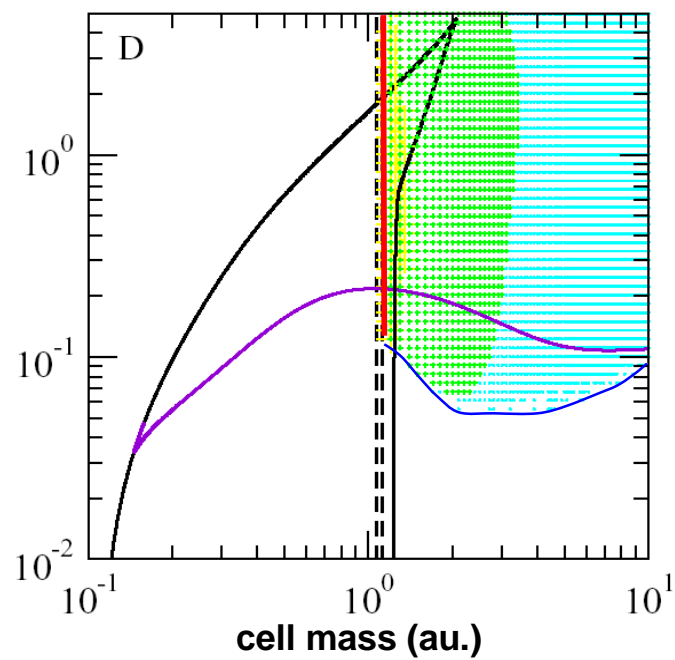
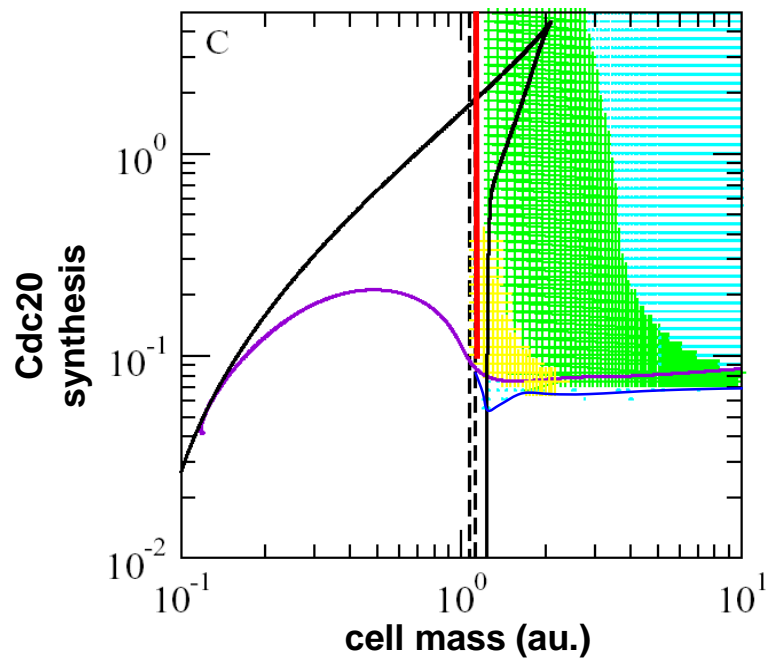
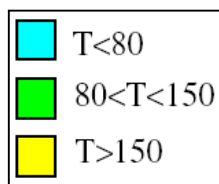
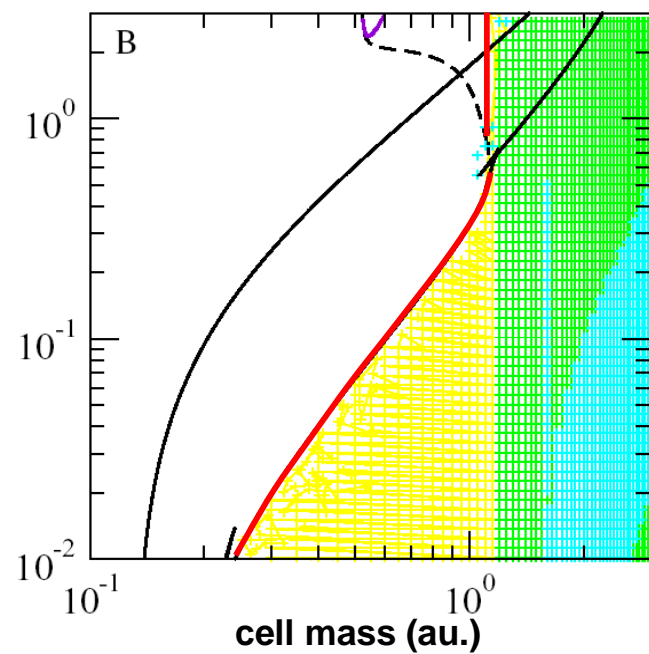
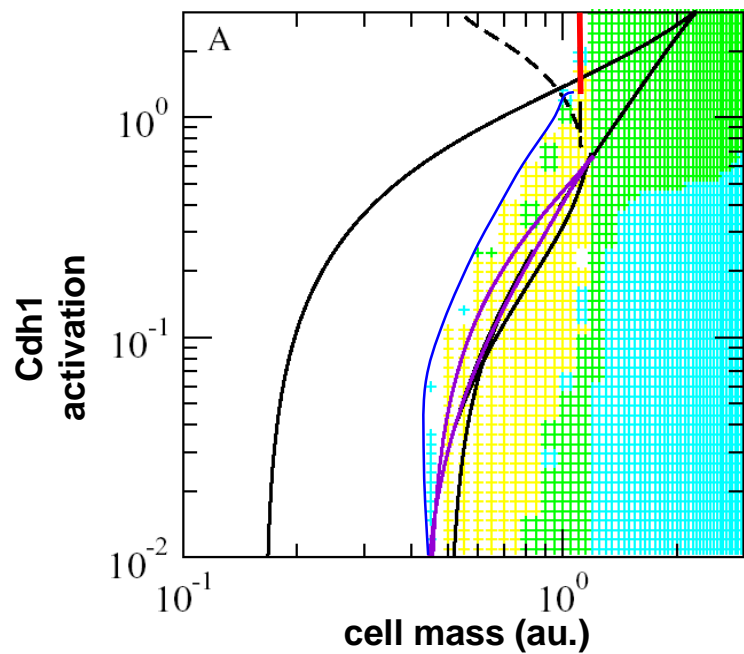


GENETICS

Cki
synthesis



PHYSIOLOGY



The Dynamical Perspective

