A simple model for the eukaryotic cell cycle

Andrea Ciliberto

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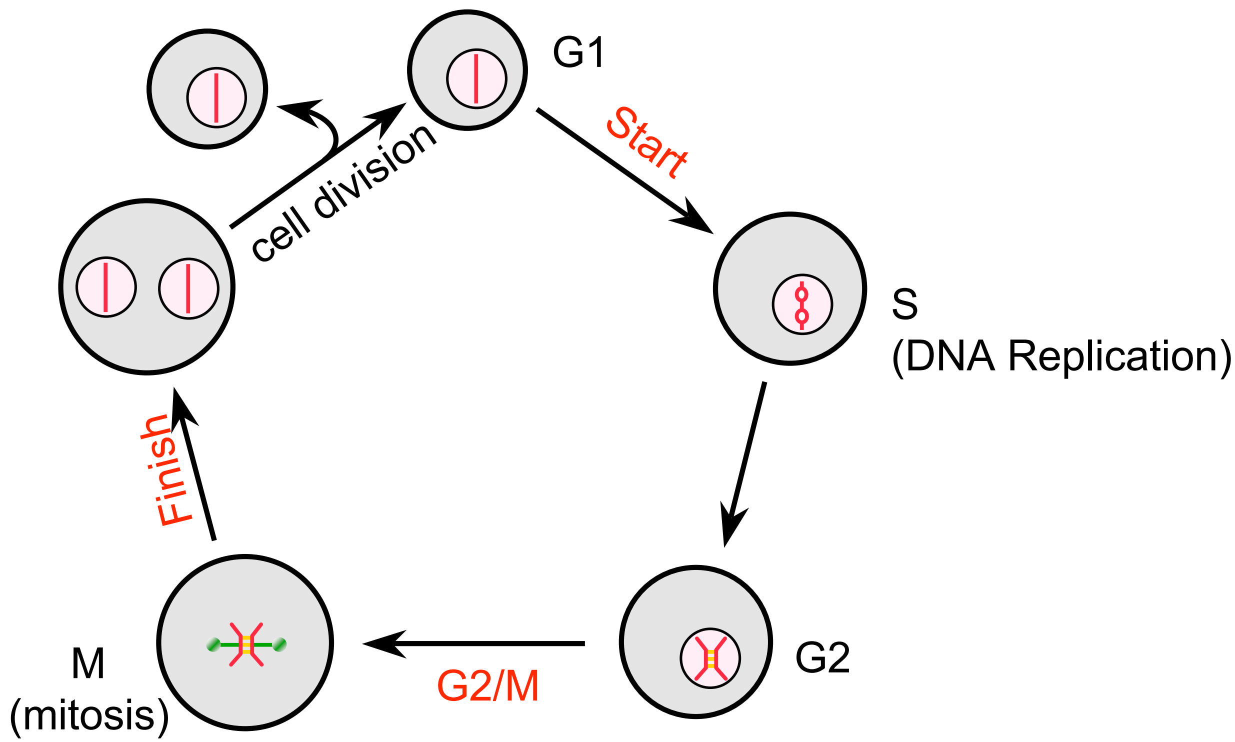
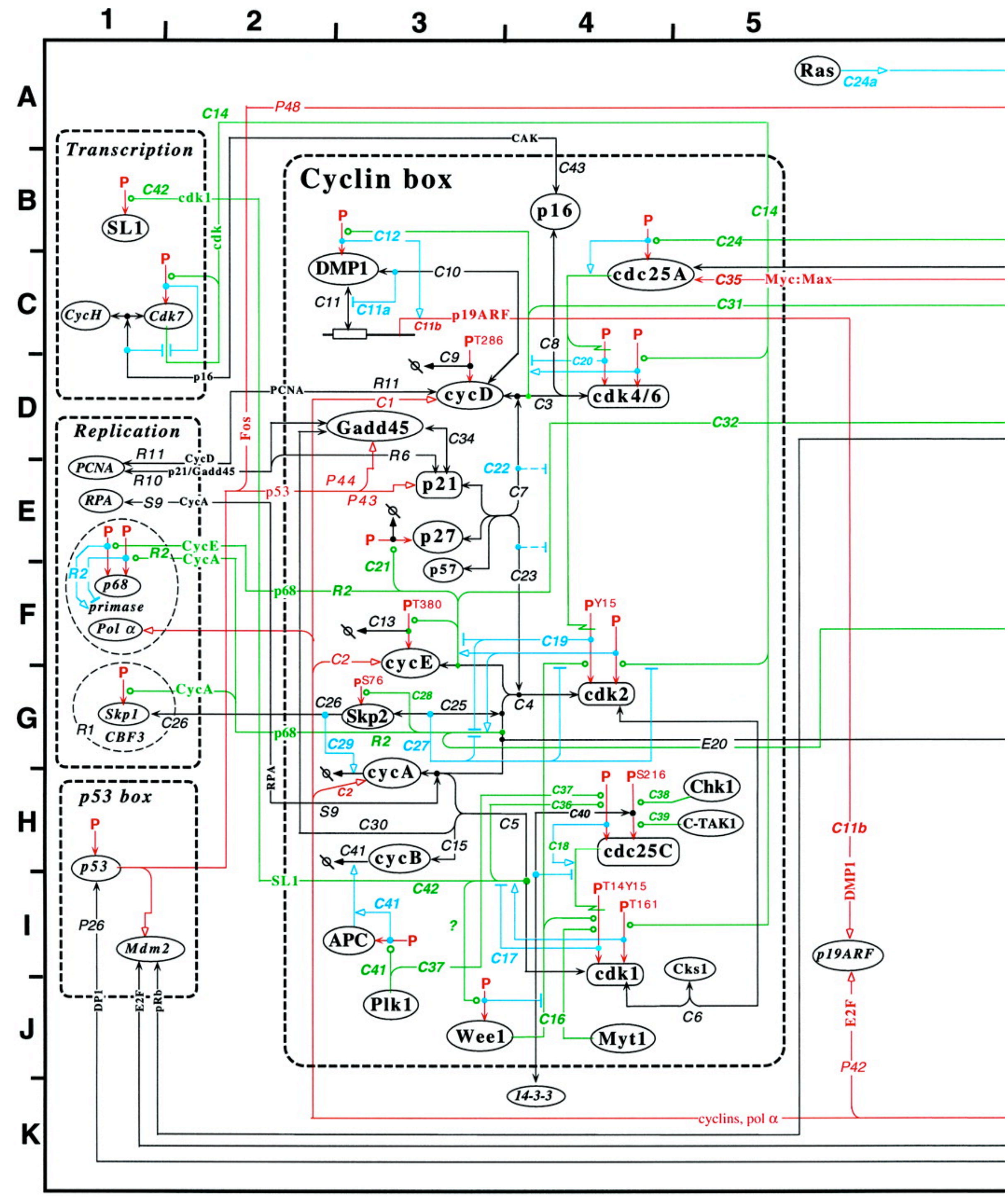
The cell division cycle





Kohn, Mol. Biol. Cell., 1999

How did we get to this mess??

Dominoes and Clocks: The Union of Two Views of the Cell Cycle

ANDREW W. MURRAY AND MARC W. KIRSCHNER

We review the recent advances in understanding transitions within the cell cycle. These have come from both genetic and biochemical approaches. We discuss the phylogenetic conservation of the mechanisms that induce mitosis and their implications for other transitions in the cell cycle.

THE CELL CYCLE IS THE SET OF EVENTS THAT IS RESPONSIBLE for the duplication of the cell. The recent advances in our understanding of the cell cycle have come from two approaches. Geneticists attempted to understand the cell cycle by analyzing mutations that arrested the cell cycle of somatic cells at specific points, whereas embryologists and physiologists examined natural points of cell cycle arrest and the agents that induced the embryonic cell cycle to proceed.

The genetic approach to the somatic cell cycle evolved from prokaryotic genetics in the 1950s and 1960s. With genetics, researchers successfully explained complicated processes, such as phage morphogenesis, as a linear sequence of events. The most extreme models of these processes suggested that they would resemble metabolic pathways: the initiation of each step in the pathway would be dependent on the completion of the preceding step, because the product of the earlier step was the substrate for the latter one; specific genes were assumed to execute each step. When this approach was applied to yeast, first in the budding yeast by Hartwell and his colleagues (*1*) and later in the fission yeast by Nurse and his colleagues (*2*), the result was a description of the cell cycle as a set of dependent reactions. The basis of this dependency is discussed in the accompanying review by Hartwell and Weinert (*3*). The physiological and embryological approach was championed by researchers who favored marine and amphibian eggs. They argued that eggs and oocytes were the simplest systems for studying the basic processes of the cell cycle, because they were specialized for rapid cell division. The result of their investigations was a description of the cell cycle as a biochemical machine that oscillated between two states, mitosis and interphase, and whose oscillations were independent of the completion of many of the cell cycle events. Initially the two views of the cell cycle, one as a set of dependent reactions (the domino theory) and the other as a biochemical oscillator (the clock theory), seemed incompatible.

The cell fusion experiments of Rao and Johnson (*4*) supported both points of view. The fusion of cells in mitosis with cells in any other state induced some form of mitotic response in the interphase nucleus and supported the embryological model of distinct mitotic and interphase cytoplasmic states, with the mitotic state dominant over all interphase states (*4*). Fusion experiments, however, also supported the idea of a dependent cell cycle, since in any fusion between two interphase cells at different stages of the cell cycle, the advanced nucleus waits for the completion of events in the retarded nucleus before progressing in the cell cycle (*4*).

In this review we discuss recent evidence from both traditions that has led to a unified view of the eukaryotic cell cycle. This synthesis suggests that a single biochemical mechanism underlies the cell cycle in all eukaryotic organisms. We have concentrated on the reactions that regulate progress through the cell cycle and do not discuss the mechanism of individual cell cycle events such as DNA synthesis or nuclear envelope breakdown and reformation.

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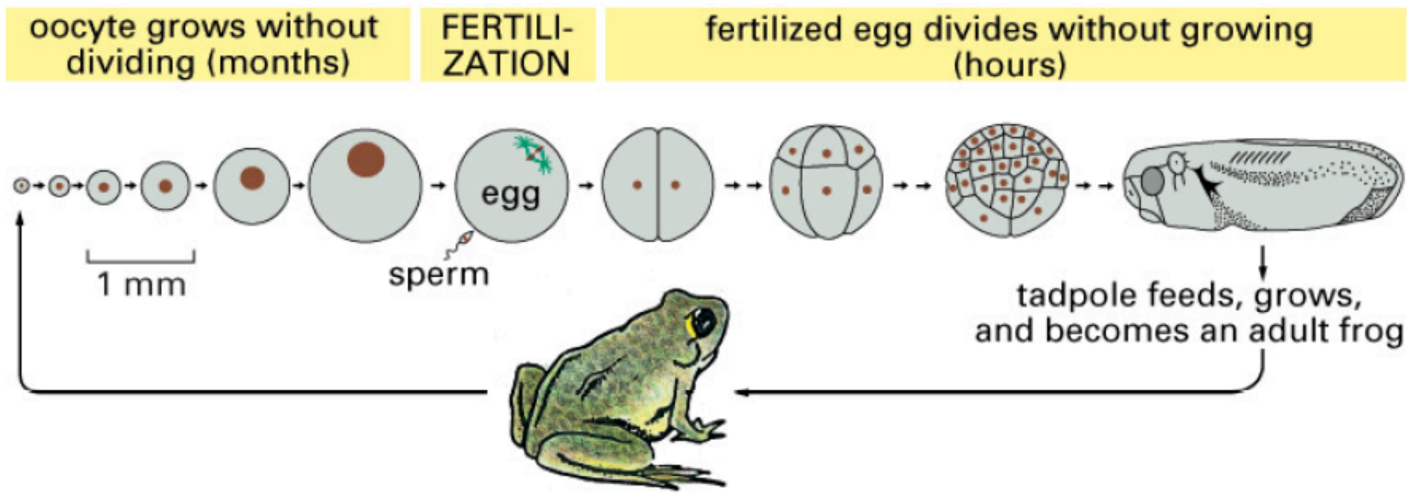
Murray and Kirschner, Science, 1989

Xenopus and the clock paradigm

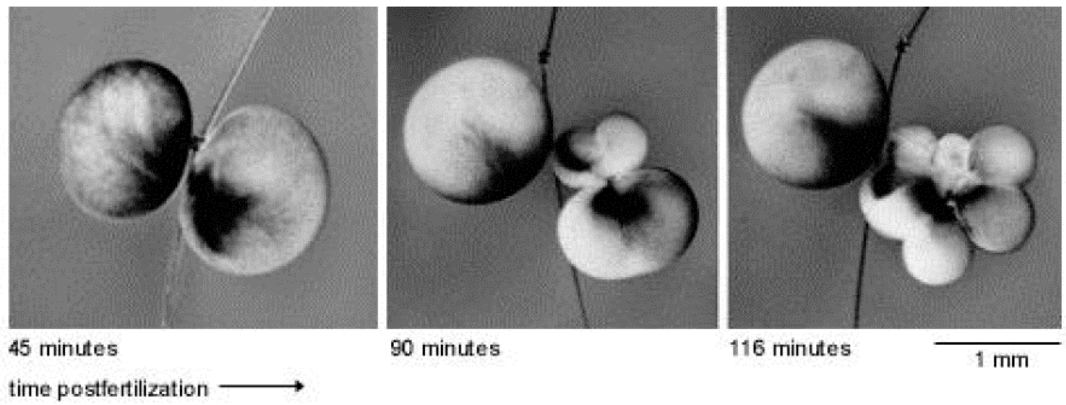


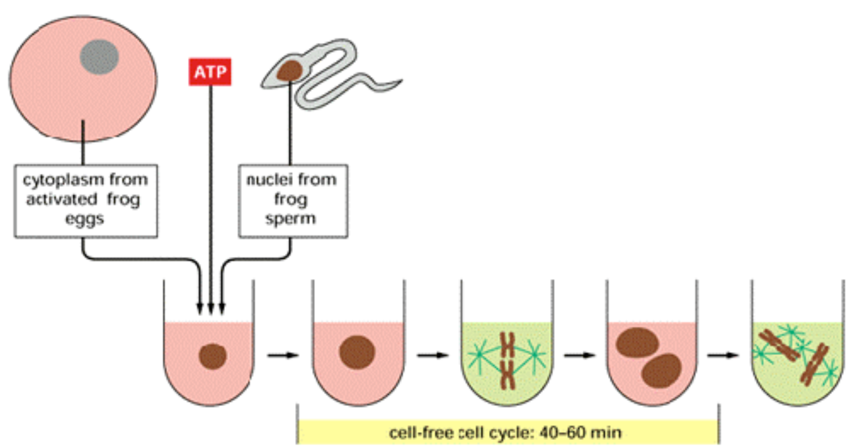
Cell mass decreases during early divisions

Alberts et a., Molecular Biology of the Cell.2002

In Xenopus oscillations progress independently of DNA presence and cell cycle events

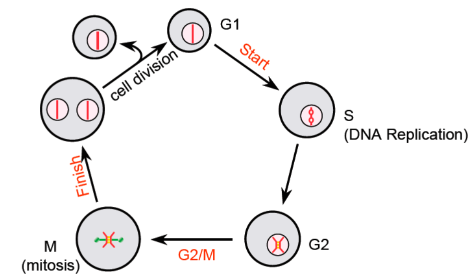
Autonomous oscillations!

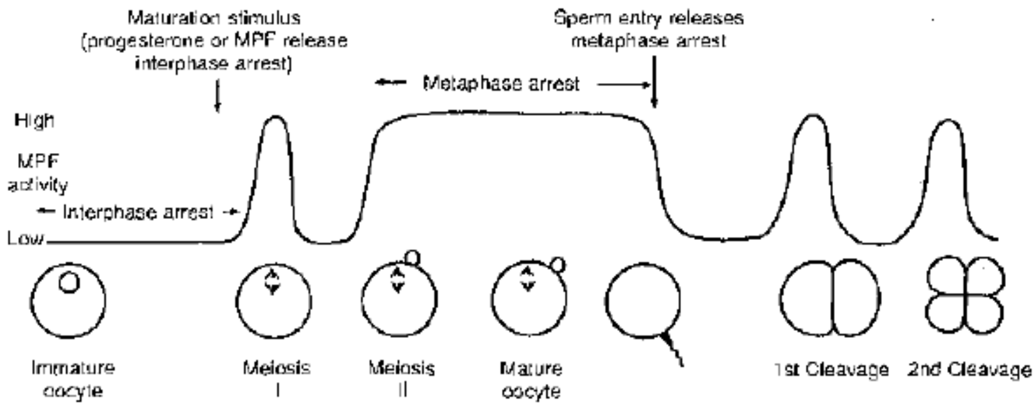




Alberts et a., Molecular Biology of the Cell.2002

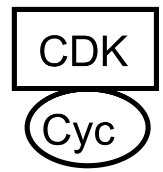
MPF, the mitosis promoting factor





Murray and Kirschner, Science, 1989

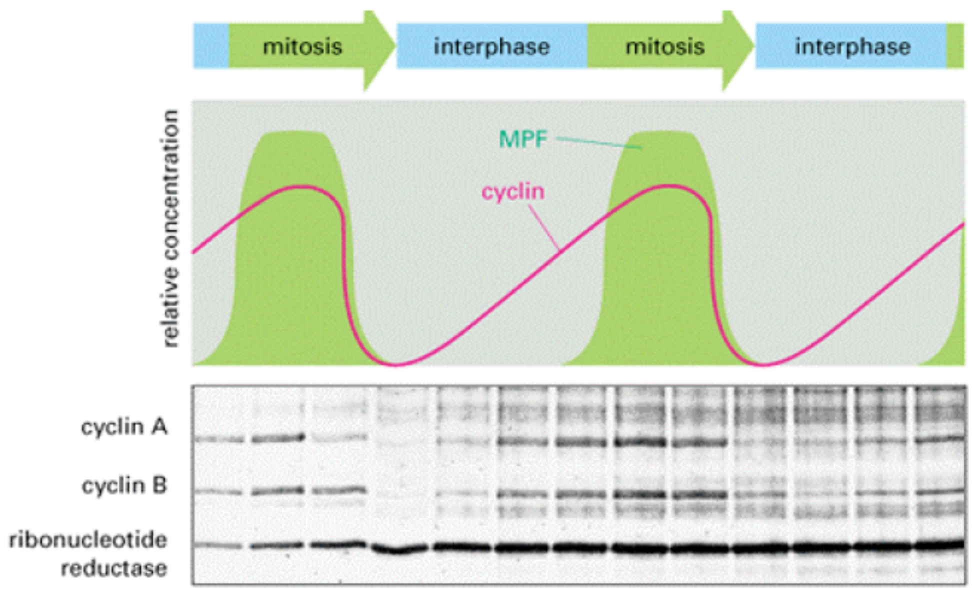
MPF is a heterodimer



cyclin dependent kinase

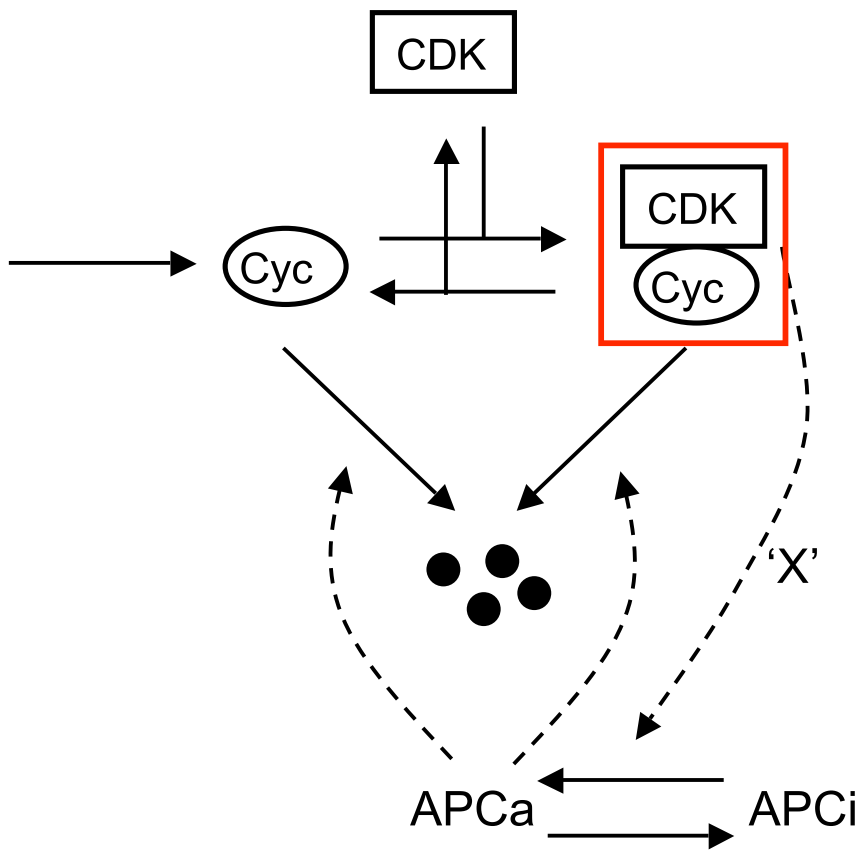
cyclin (regulatory subunit)

Only cyclin synthesis and degradation are required for *Xenopus* early cycles.

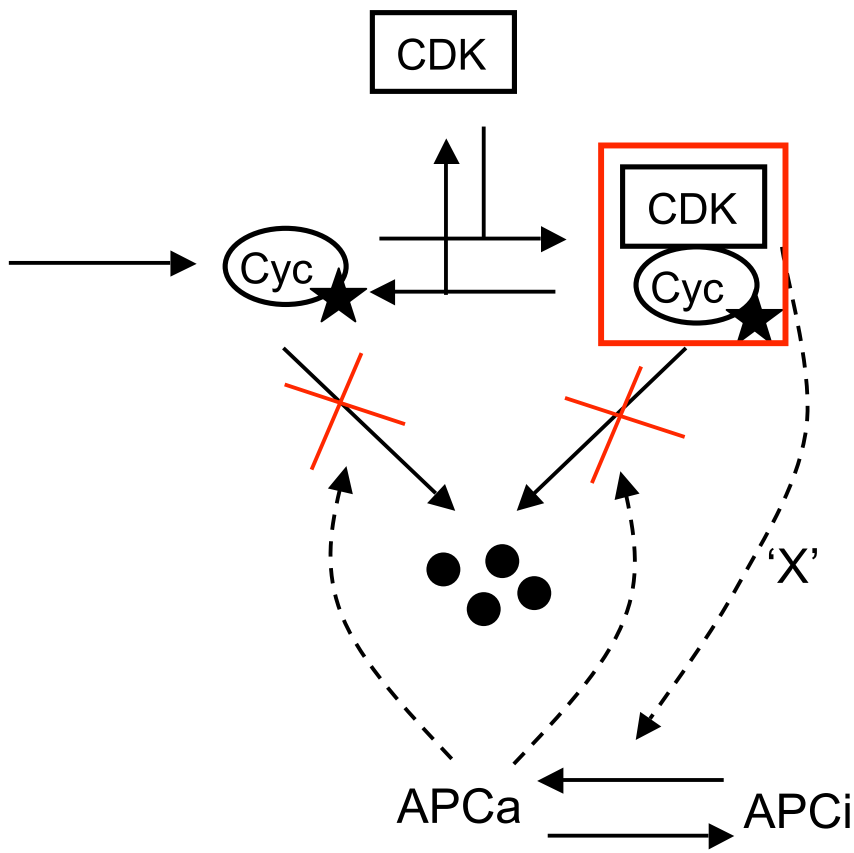


Alberts et a., Molecular Biology of the Cell.2002

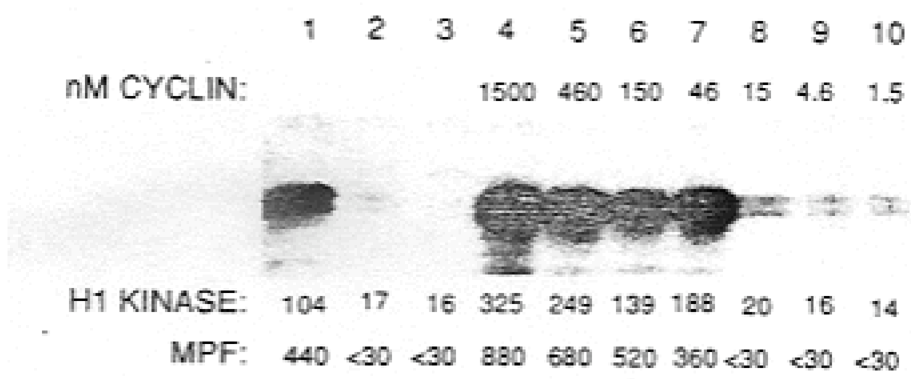
CDK is activated by cyclin binding and once activated it induces cyclin degradation



But something else must be at work...

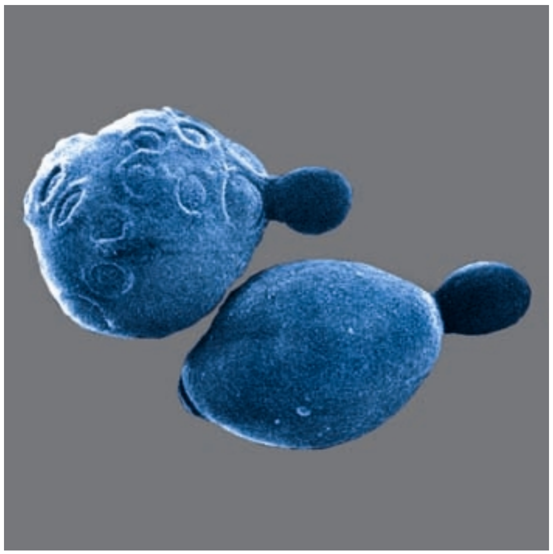


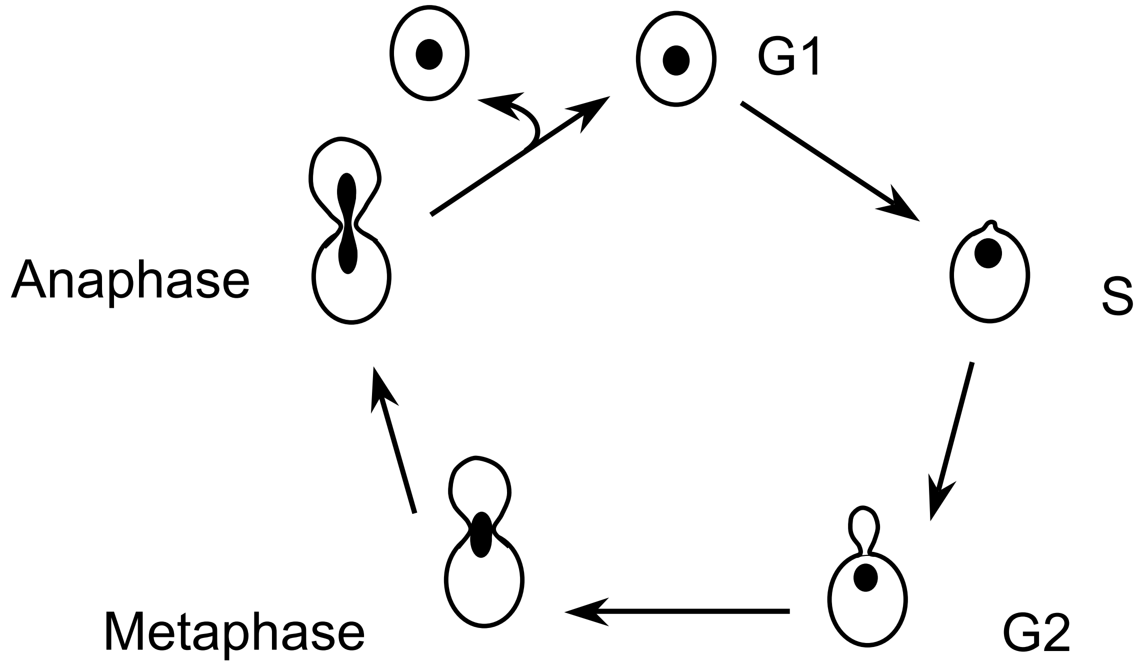
Cyclin threshold



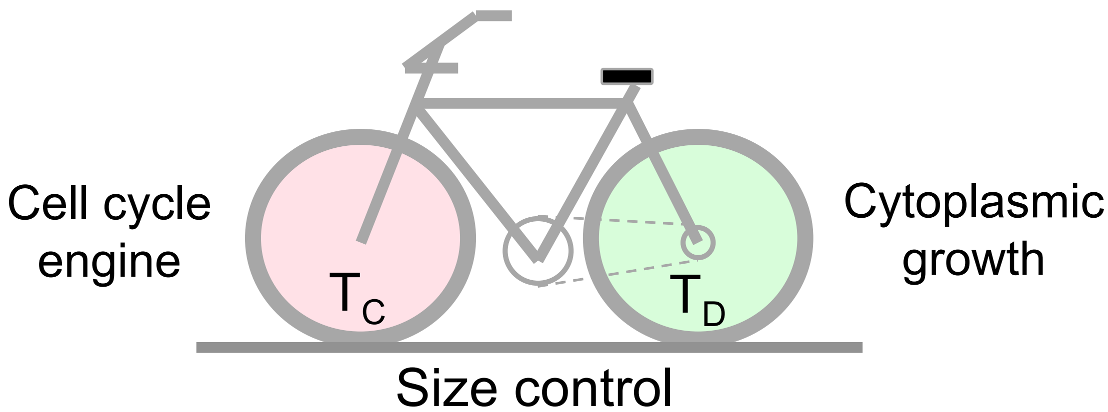
Solomon et al, Cell, 1990

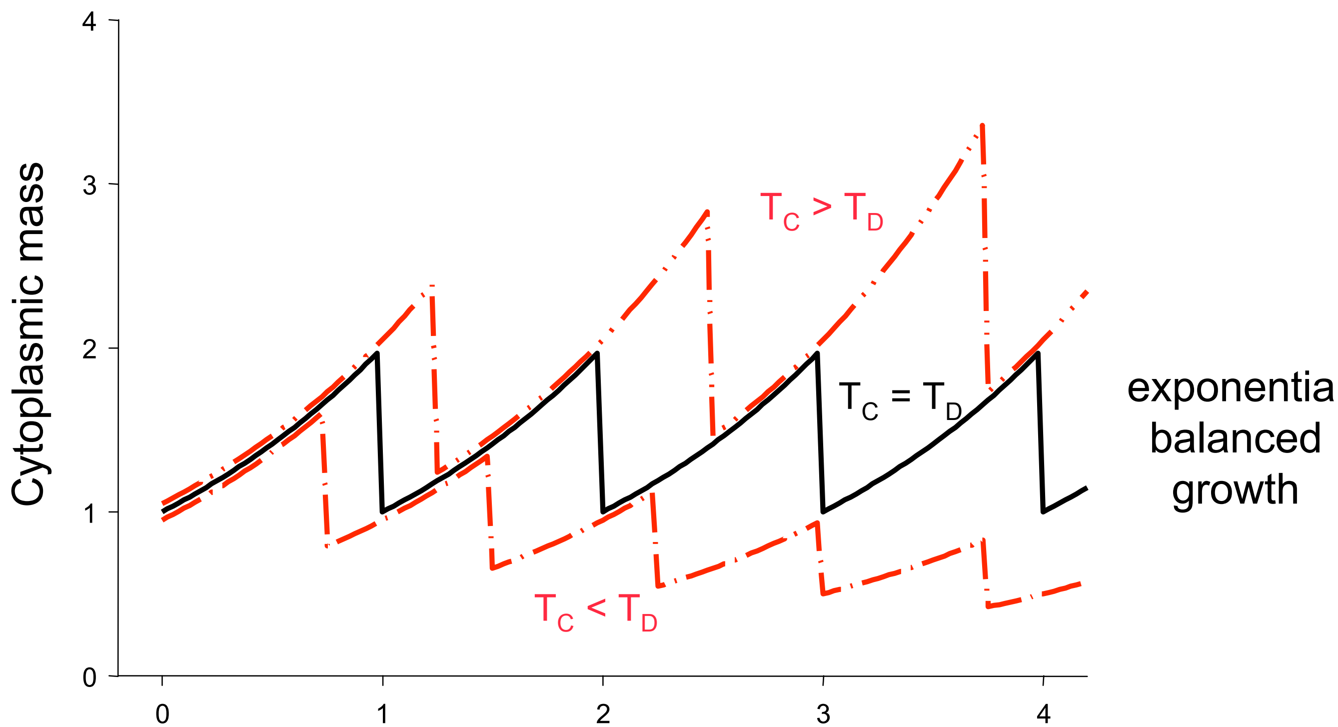
Yeast and the domino paradigm





Balanced growth and division





Cell division cycle (cdc) mutants are temperature sensitive

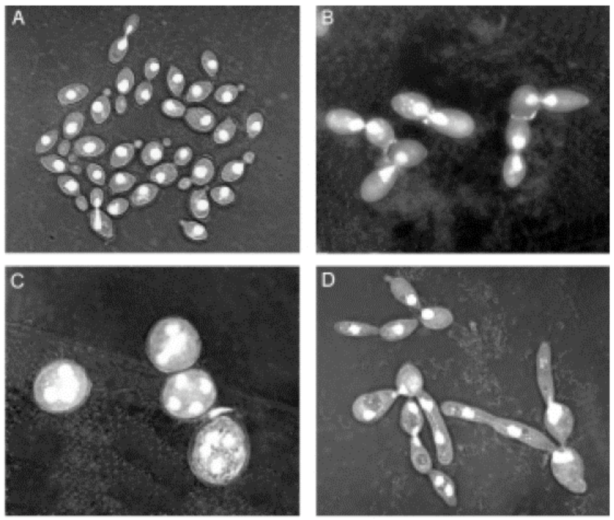


Figure 5. Normal cells and *cdc* mutant cells several hours after incubation at the restrictive temperature. (A) wild type, (B) *cdc8* (C) *cdc24* (D) *cdc10*.

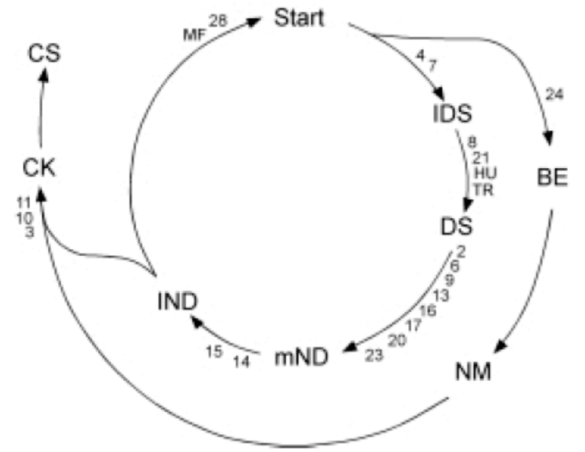
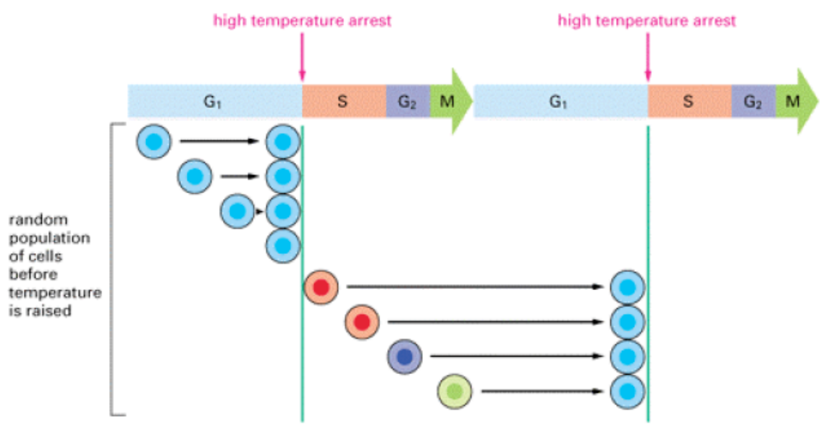


Figure 6. A pathway of gene controlled events in the *S. cerevisiae* cell cycle. Numbers refer to *cdc* genes. Abbreviations are: iDS, initiation of DNA synthesis, DS, DNA synthesis, mND, medial nuclear division; lND, late nuclear division; BE, bud emergence; NM, nuclear migration; CK, cytokinesis; CS cell separation; MF mating factor. Reprinted from ref 7 with permission.

Hartwell, Genetics, 1991

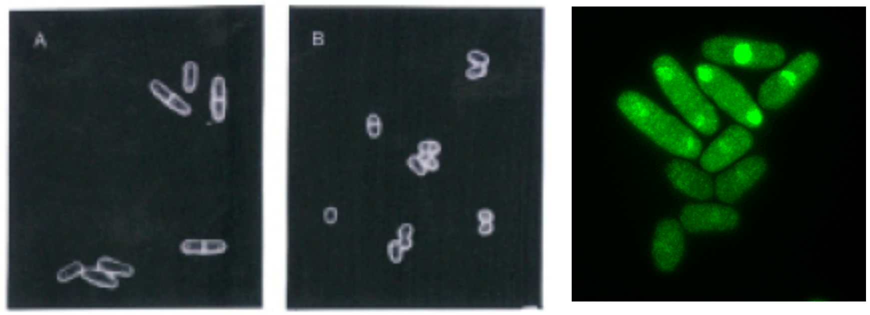


Alberts et a., Molecular Biology of the Cell.2002

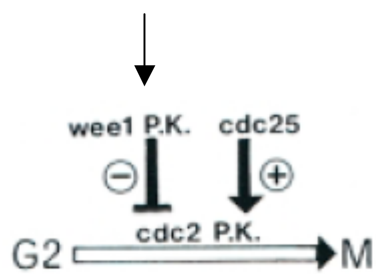
Wee1 controls a rate limiting step in the cell cycle

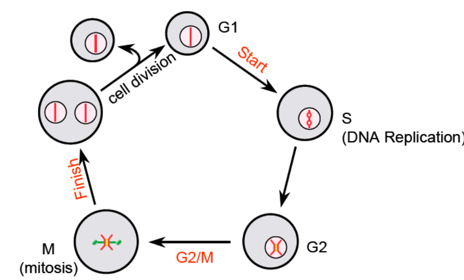
Cell division and cell growth are coupled

wild type | *wee1* | *cdc25*



unreplicated DNA





Nurse, Noble lecture, 2000

Basic cell cycle properties

- Cell physiology-

- Coupling of mass growth and cell division.

- Once the cell enters the cycle,it is commited to finish it: irreversibility.

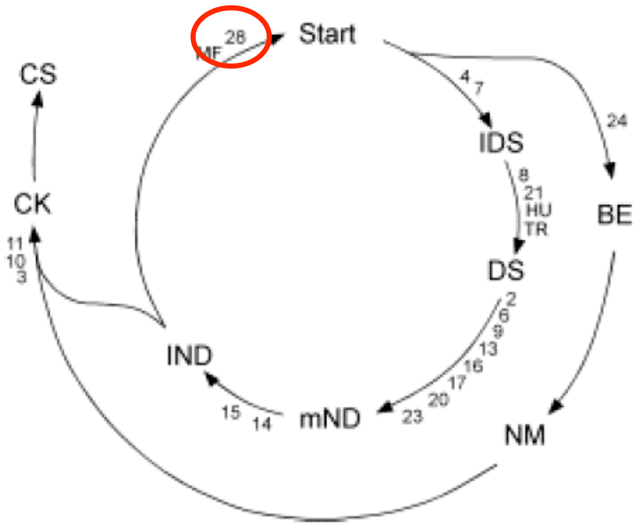
- The cell halts during cell cycle progression if something has gone wrongly.

-Molecular network-

-Oscillations of MPF drive cells into and out of mitosis.

- Cdc28 activity is controlled by Wee1 (negative) and Cdc25 (positive).

Dominoes and clocks: Cdc28 is the budding yeast homologous of MPF's catalytic subunit



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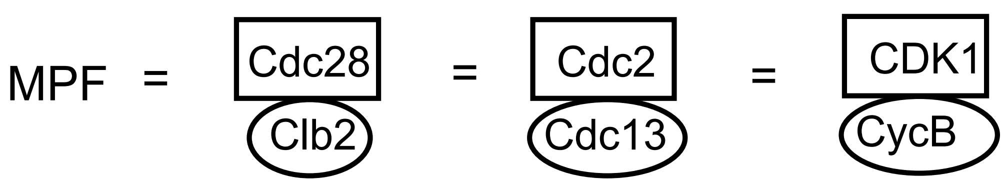
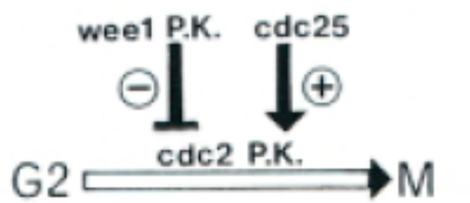
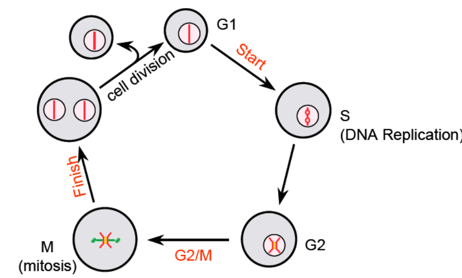
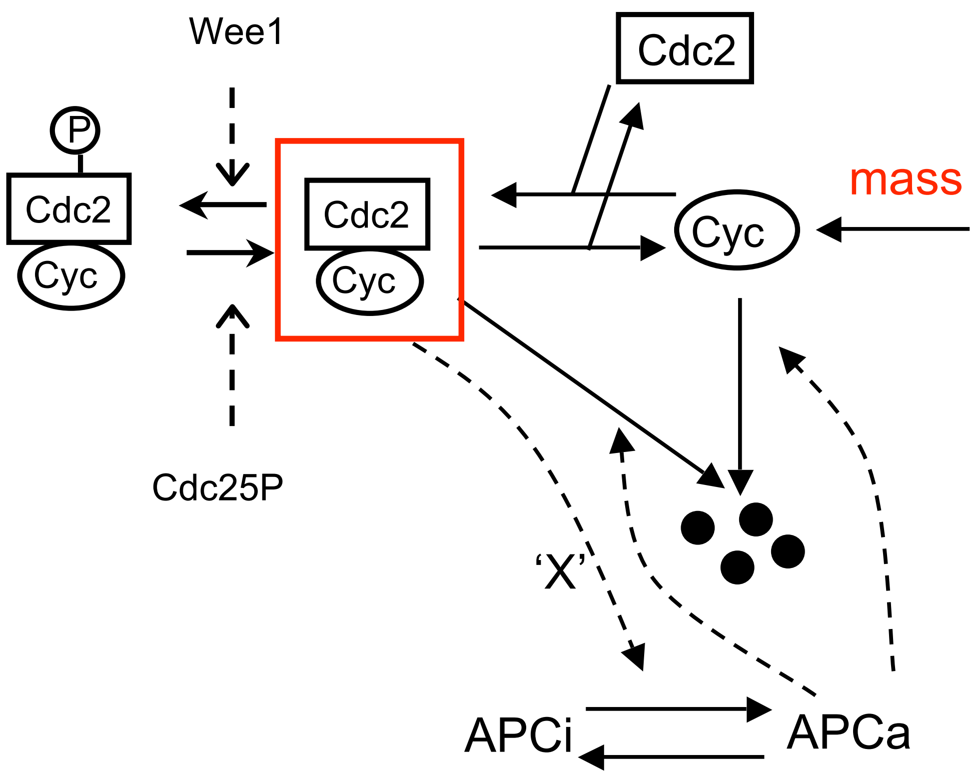


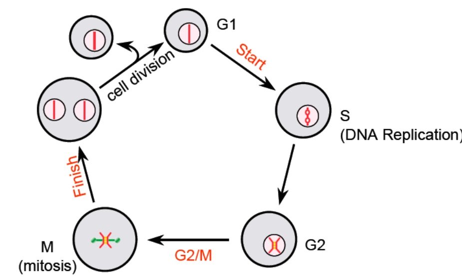
Phosphorylation as well as cyclin binding controls MPF activity

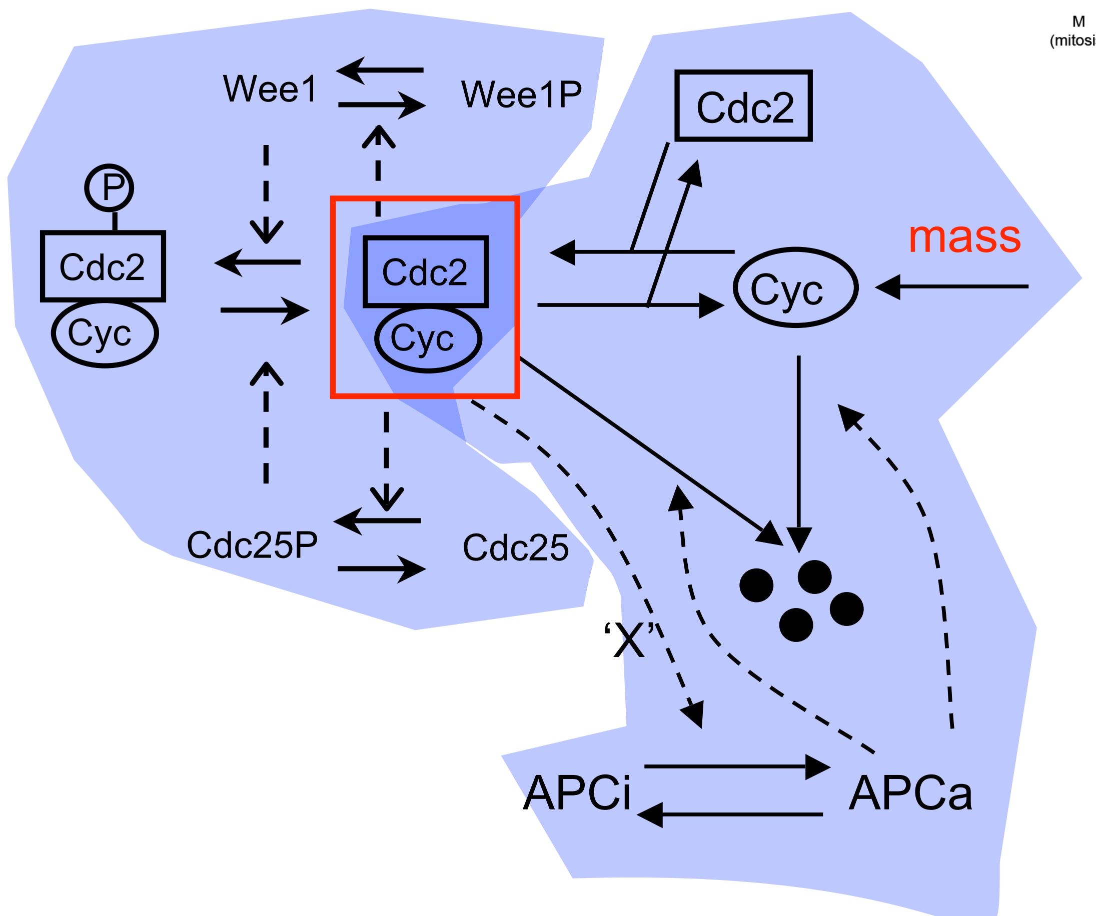




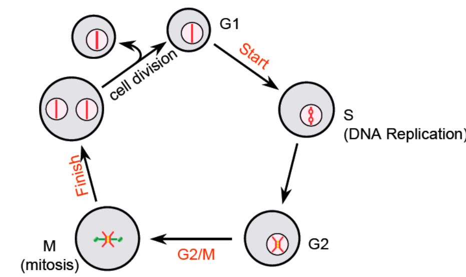


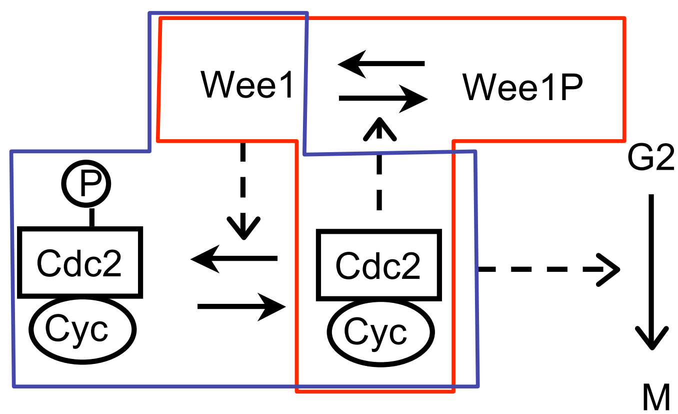
Phosphorylation as well as cyclin binding controls MPF activity





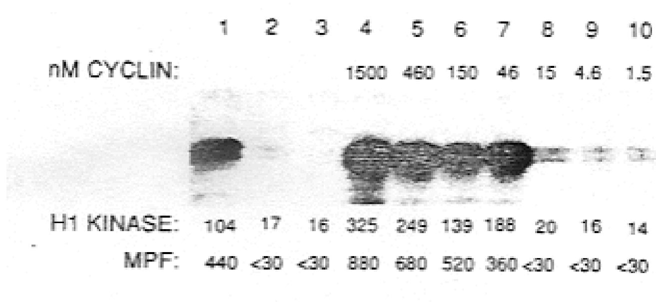
Isolation and analysis of a positive feedback: the network...





Notice, here no cyclin synthesis, no cyclin degradation!!

...and the physiology



Solomon et al, Cell, 1990

Part II
Standard laws of biochemical kinetics applied to molecular networks

Law of Mass Action: forward reaction

$$\text{pMPF} \xrightarrow{k_a} \text{MPF}$$

$$\frac{dMPF}{dt} = k_a \cdot pMPF$$

$$pMPF = MPF_{tot} - MPF$$

$$\frac{dMPF}{dt} = k_a \cdot (MPF_{tot} - MPF)$$

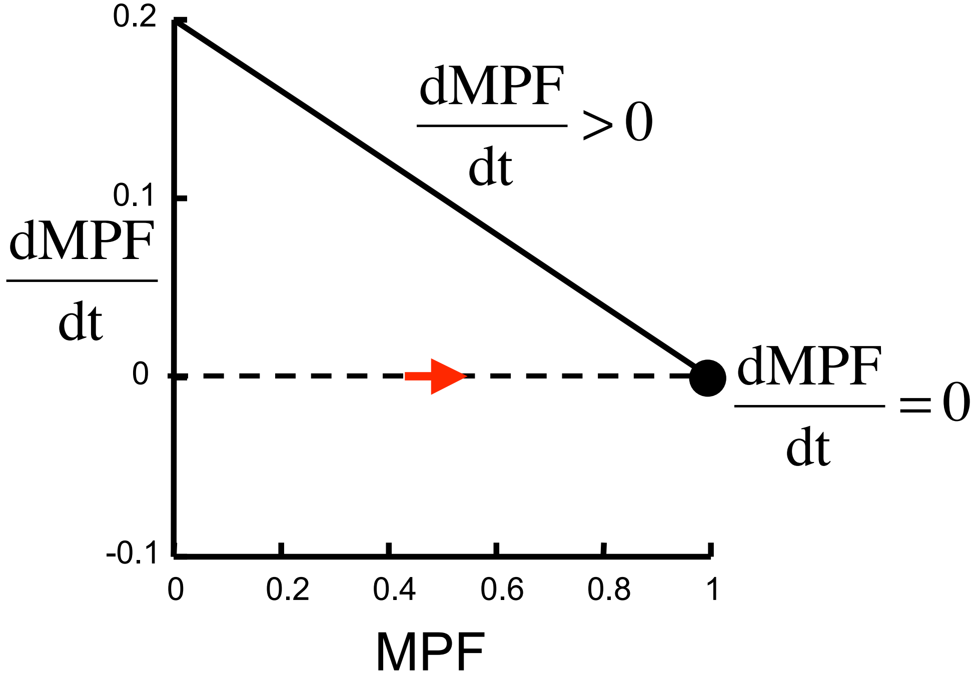
Steady State solution (MPF^{SS})

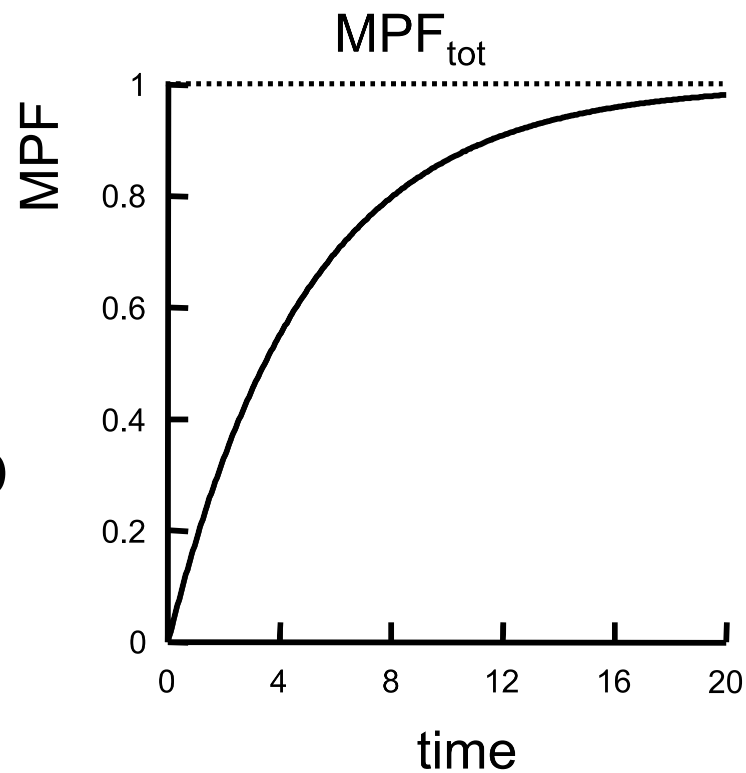
$$\frac{dMPF}{dt} = 0$$

$$MPF^{SS} = MPF_{tot}$$

Notice: no dimer, only MPF. Cdk is supposed to be present in excess throughout the cycle. Increasing MPF total mimics an increase in cyclin total.

$$\frac{dMPF}{dt} = k_a \cdot (MPF_{tot} - MPF)$$





Law of Mass Action: reversible reaction

$$\text{pMPF} \underset{k_i}{\overset{k_a}{\rightleftharpoons}} \text{MPF}$$

$$\frac{dMPF}{dt} = k_a \cdot pMPF - k_i \cdot MPF$$

Steady State solution

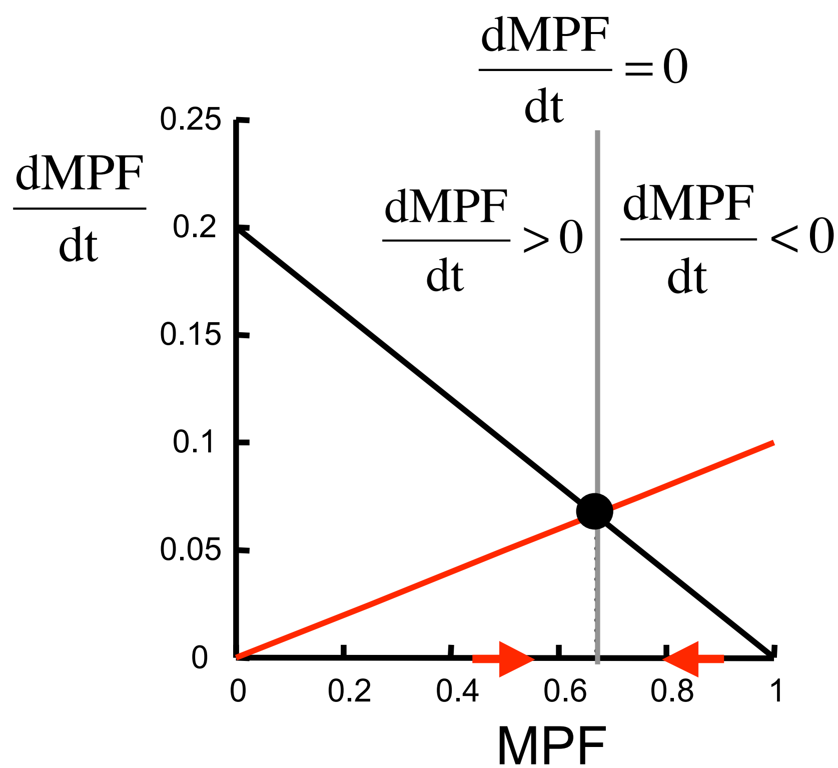
$$\frac{dMPF}{dt} = 0$$

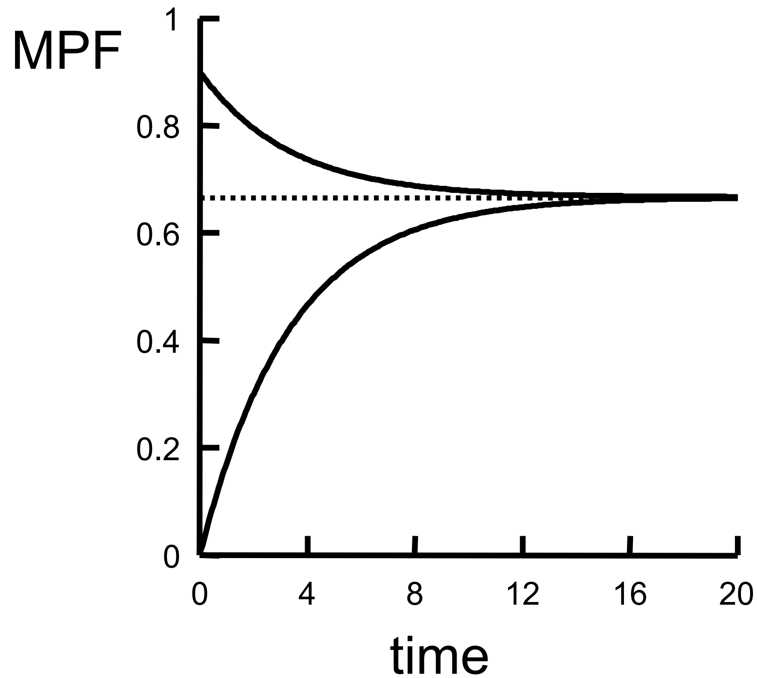
$$MPF^{SS} = \frac{k_a \cdot MPF_{tot}}{k_a + k_i}$$

$$\mathrm{pMPF} \underset{k_i}{\overset{k_a}{\rightleftharpoons}} \mathrm{MPF}$$

$$\frac{dMPF}{dt} = \underbrace{k_a \cdot (MPF_{tot} - MPF)}_{\text{production}} - \underbrace{k_i \cdot MPF}_{\text{elimination}}$$

production + elimination -





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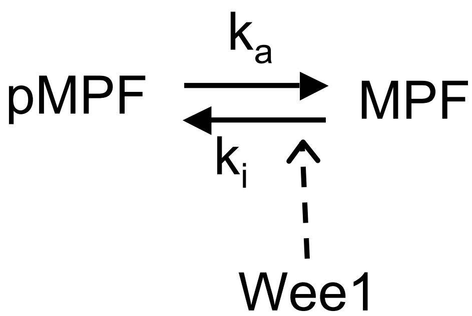
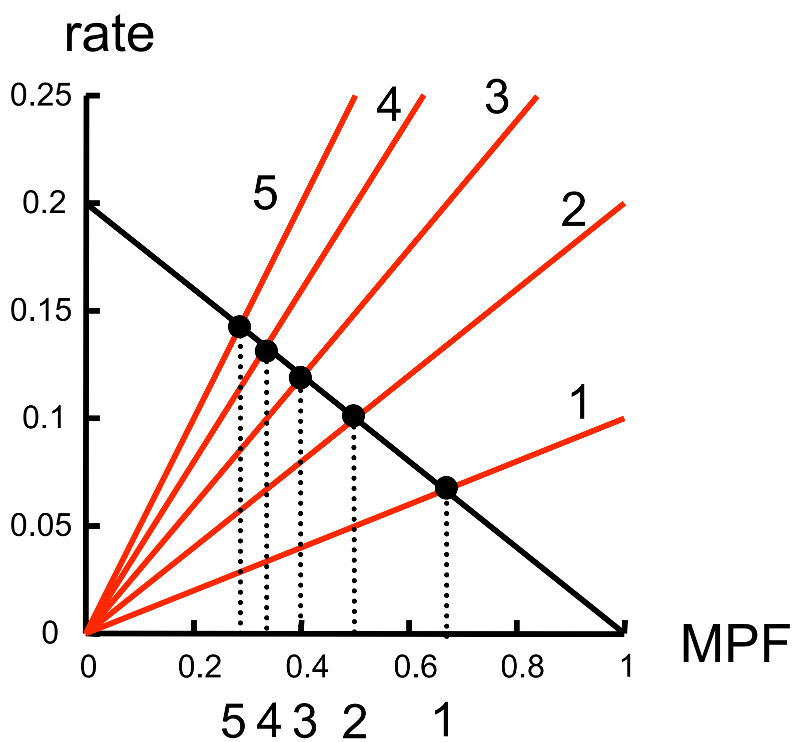
Law of Mass Action:
catalyzed reversible reaction



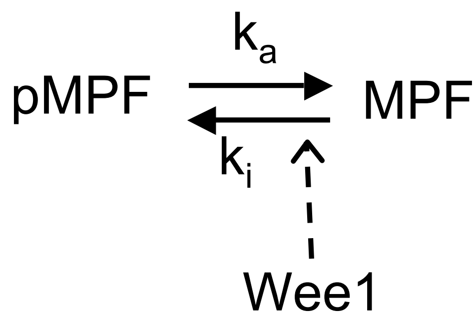
$$\frac{dMPF}{dt} = \underbrace{k_a \cdot (MPF_{tot} - MPF)}_{\text{production}} - \underbrace{k_i \cdot MPF \cdot Wee1}_{\text{elimination}}$$

production +

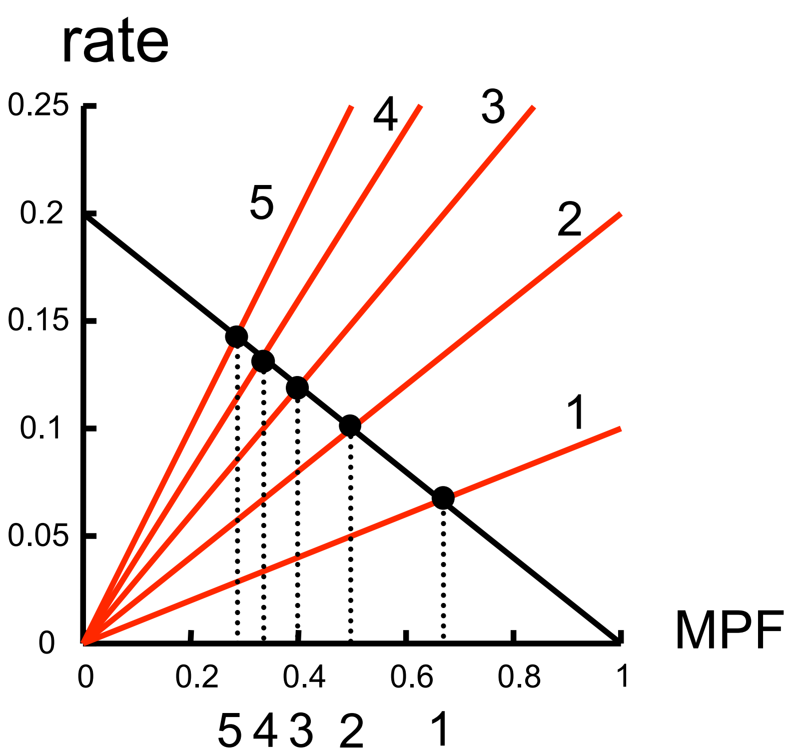
elimination -

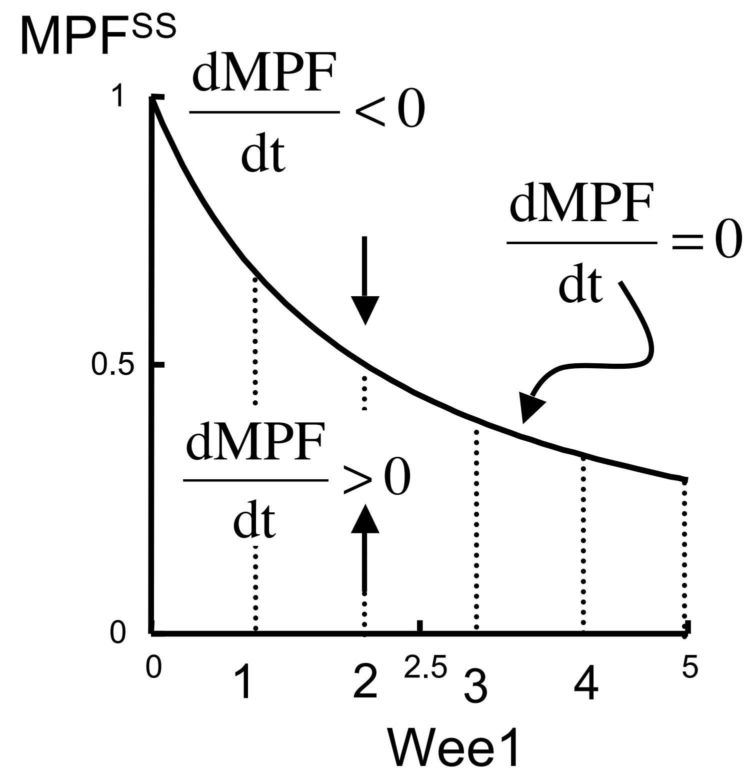


Nullclines

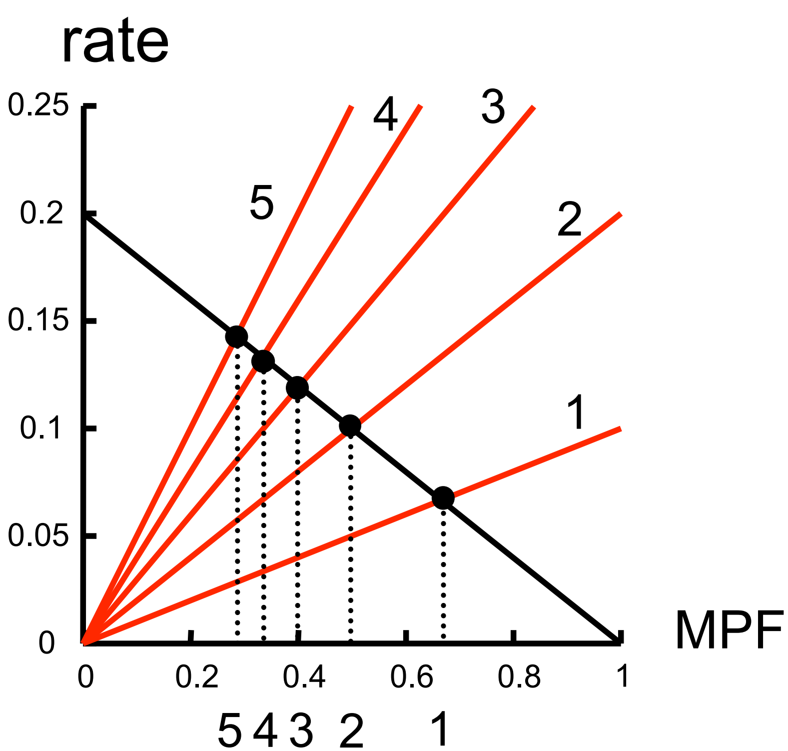


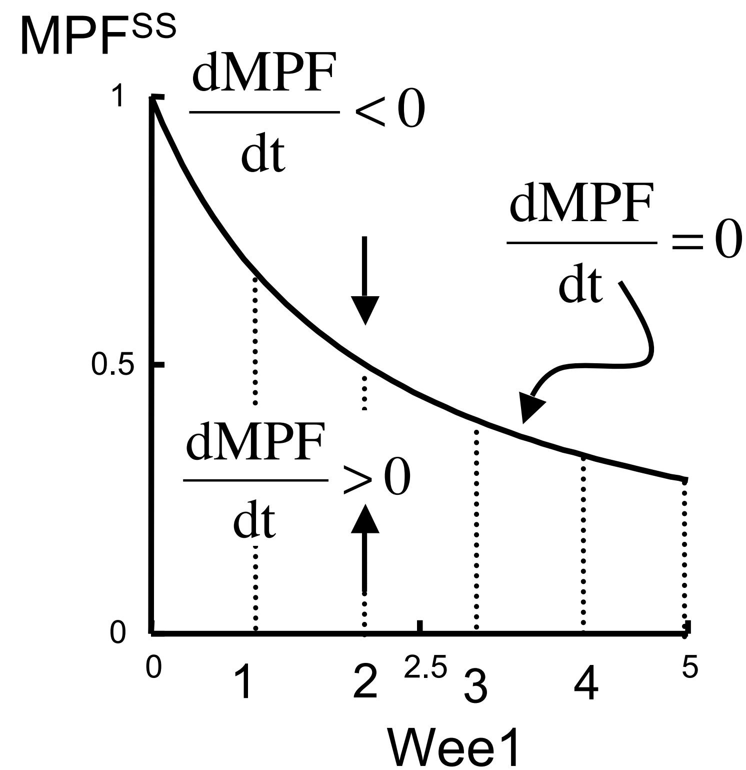
$$\frac{dMPF}{dt} = k_a \cdot \underbrace{(MPF_{tot} - MPF)}_{\text{production } +} - \underbrace{k_i \cdot MPF \cdot Wee1}_{\text{elimination } -}$$





What happens if MPF total increases?





Michaelis-Menten: forward reaction

$$\text{Wee1P} \xrightarrow{k_{wa}} \text{Wee1}$$

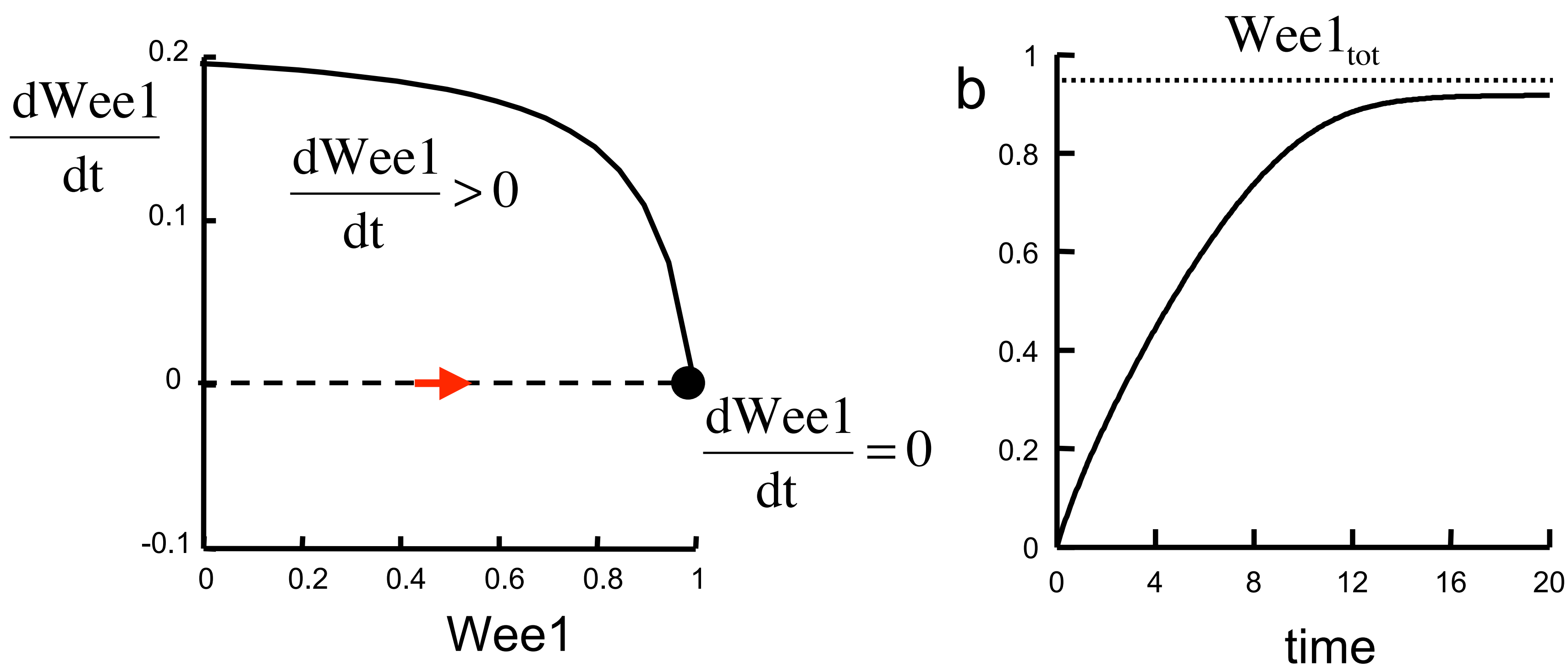
$$\frac{d\text{Wee1}}{dt} = \frac{k_{wa} \cdot \text{Wee1P}}{J + \text{Wee1P}}$$

$$\frac{d\text{Wee1}}{dt} = \frac{k_{wa} \cdot (\text{Wee1}_{tot} - \text{Wee1})}{J + (\text{Wee1}_{tot} - \text{Wee1})}$$

Steady State solution

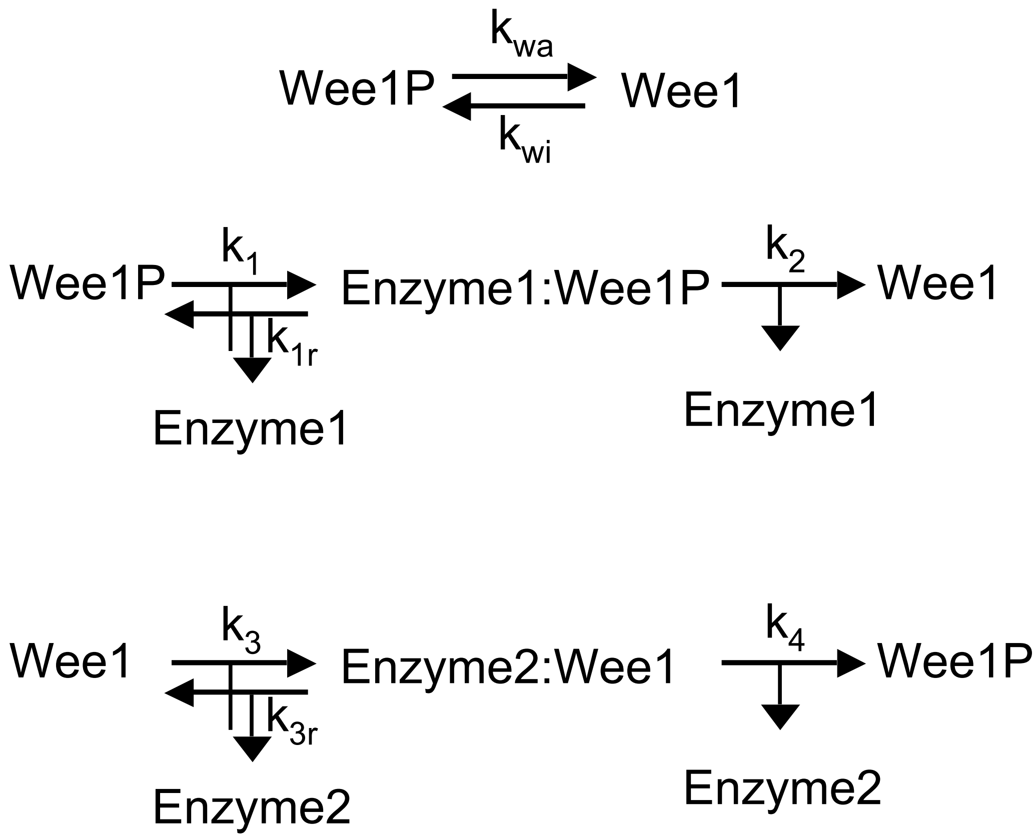
$$\frac{d\text{Wee1}}{dt} = 0$$

$$\text{Wee1}^{SS} = \text{Wee1}_{tot}$$



dWee1/dt
0.2
0.1
0
-0.1
dWee1/dt > 0
dWee1/dt = 0
0
0.2
0.4
0.6
0.8
1
Wee1
b
Wee1tot
1
0.8
0.6
0.4
0.2
0
0
4
8
12
16
20
time

Michaelis-Menten: reversible reaction



Proc. Natl. Acad. Sci. USA
Vol. 78, No. 11, pp. 6840–6844, November 1981
Biochemistry

An amplified sensitivity arising from covalent modification in biological systems

(protein modification/metabolic regulation/switch mechanism/enzyme cascades)

ALBERT GOLDBETER† AND DANIEL E. KOSHLAND, JR.

Department of Biochemistry, University of California, Berkeley, California 94720

Contributed by Daniel E. Koshland, Jr., August 11, 1981

if [enzym1$_{TOT}$], [enzyme2$_{TOT}$] << [Wee1$_{TOT}$]

$$k_{wa} = [\text{enzyme1}_{TOT}]k_2$$

$$k_{wi} = [\text{enzyme2}_{TOT}]k_4$$

$$\frac{dWee1}{dt} = \frac{k_{wa} \cdot (Wee1_{tot} - Wee1)}{J + Wee1_{tot} - Wee1} - \frac{k_{wi} \cdot Wee1}{J + Wee1}$$

production
+

elimination
-

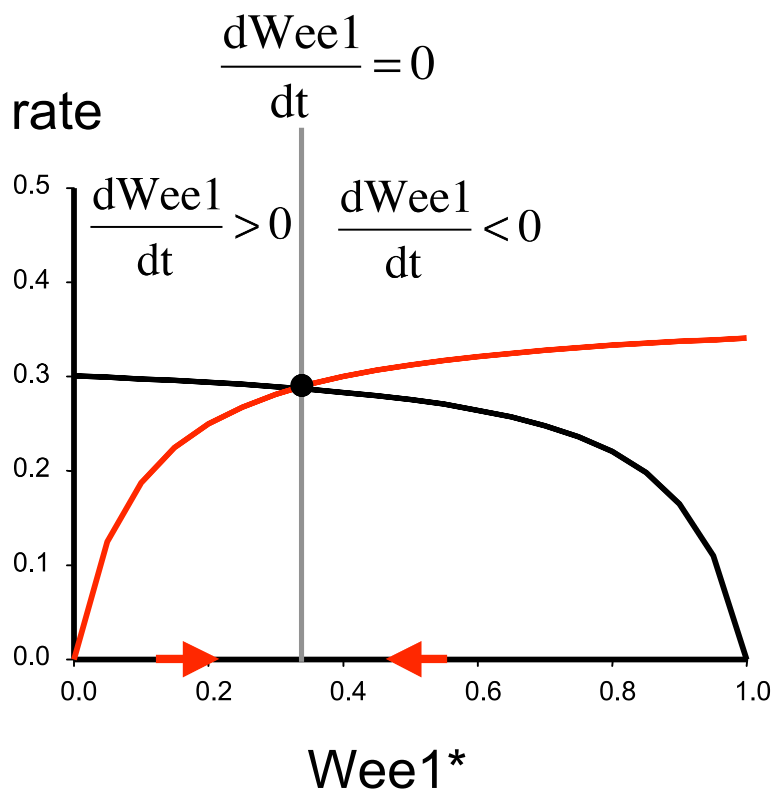
Michaelis-Menten: reversible reaction

$$\text{Wee1P} \underset{k_{wi}}{\overset{k_{wa}}{\rightleftharpoons}} \text{Wee1}$$

$$\frac{d\text{Wee1}}{dt} = \frac{k_{wa} \cdot (\text{Wee1}_{tot} - \text{Wee1})}{J + \text{Wee1}_{tot} - \text{Wee1}} - \frac{k_{wi} \cdot \text{Wee1}}{J + \text{Wee1}}$$

production +

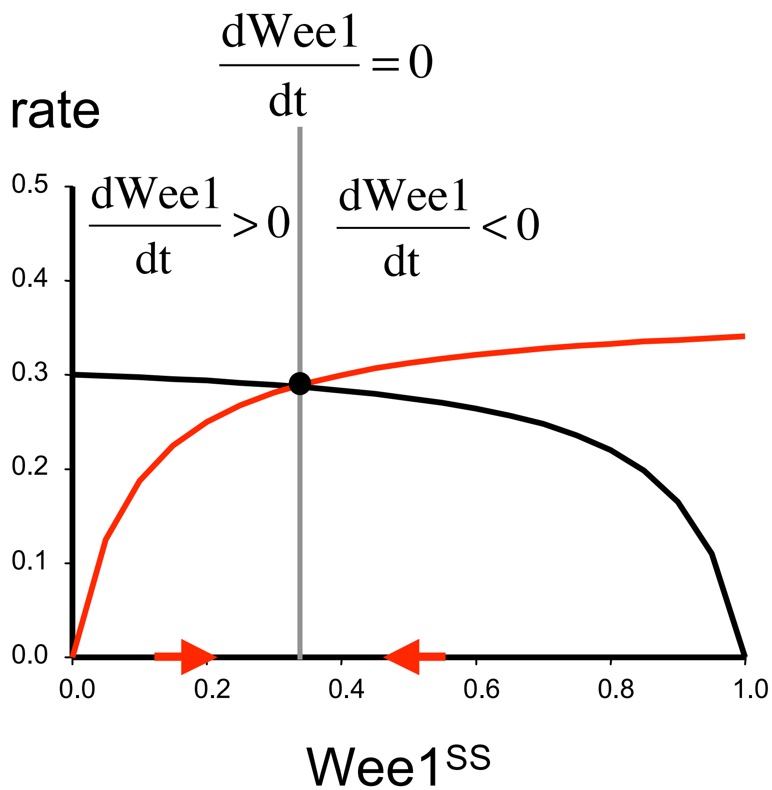
elimination -

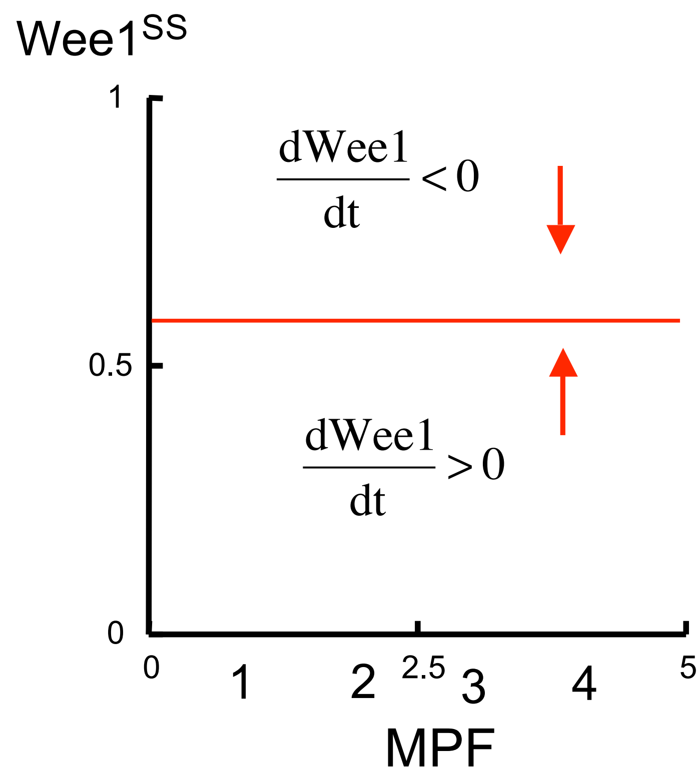


Nullclines

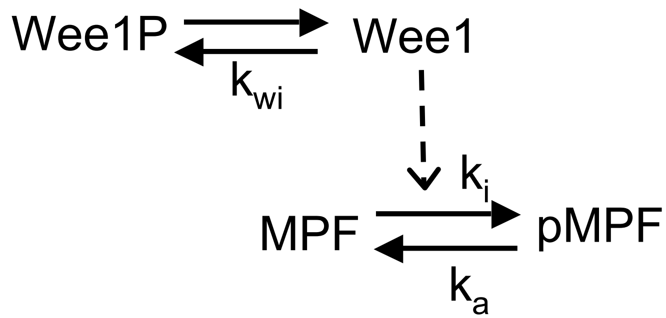
$$\mathrm{Wee1P} \underset{k_{wi}}{\overset{k_{wa}}{\rightleftharpoons}} \mathrm{Wee1}$$

$$\frac{d\mathrm{Wee1}}{dt} = \underbrace{\frac{k_{wa} \cdot (\mathrm{Wee1}_{tot} - \mathrm{Wee1})}{J + \mathrm{Wee1}_{tot} - \mathrm{Wee1}}}_{\text{production } +} - \underbrace{\frac{k_{wi} \cdot \mathrm{Wee1}}{J + \mathrm{Wee1}}}_{\text{elimination } -}$$



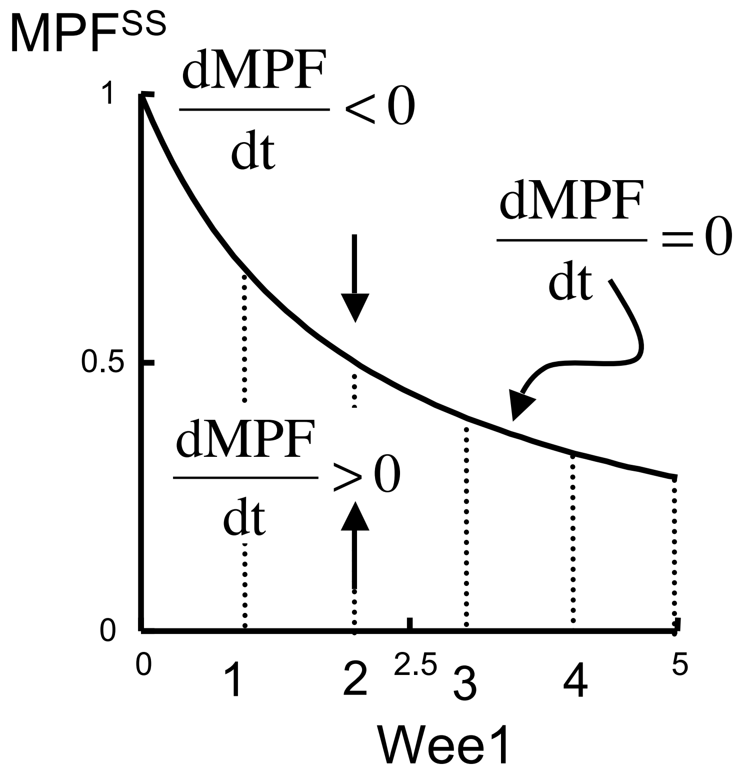


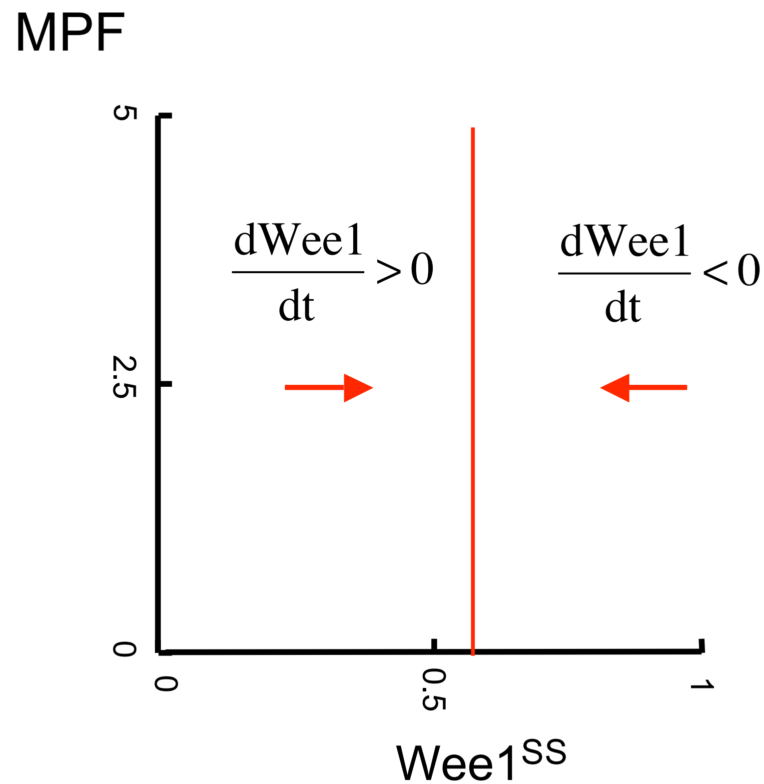
Phase plane analysis

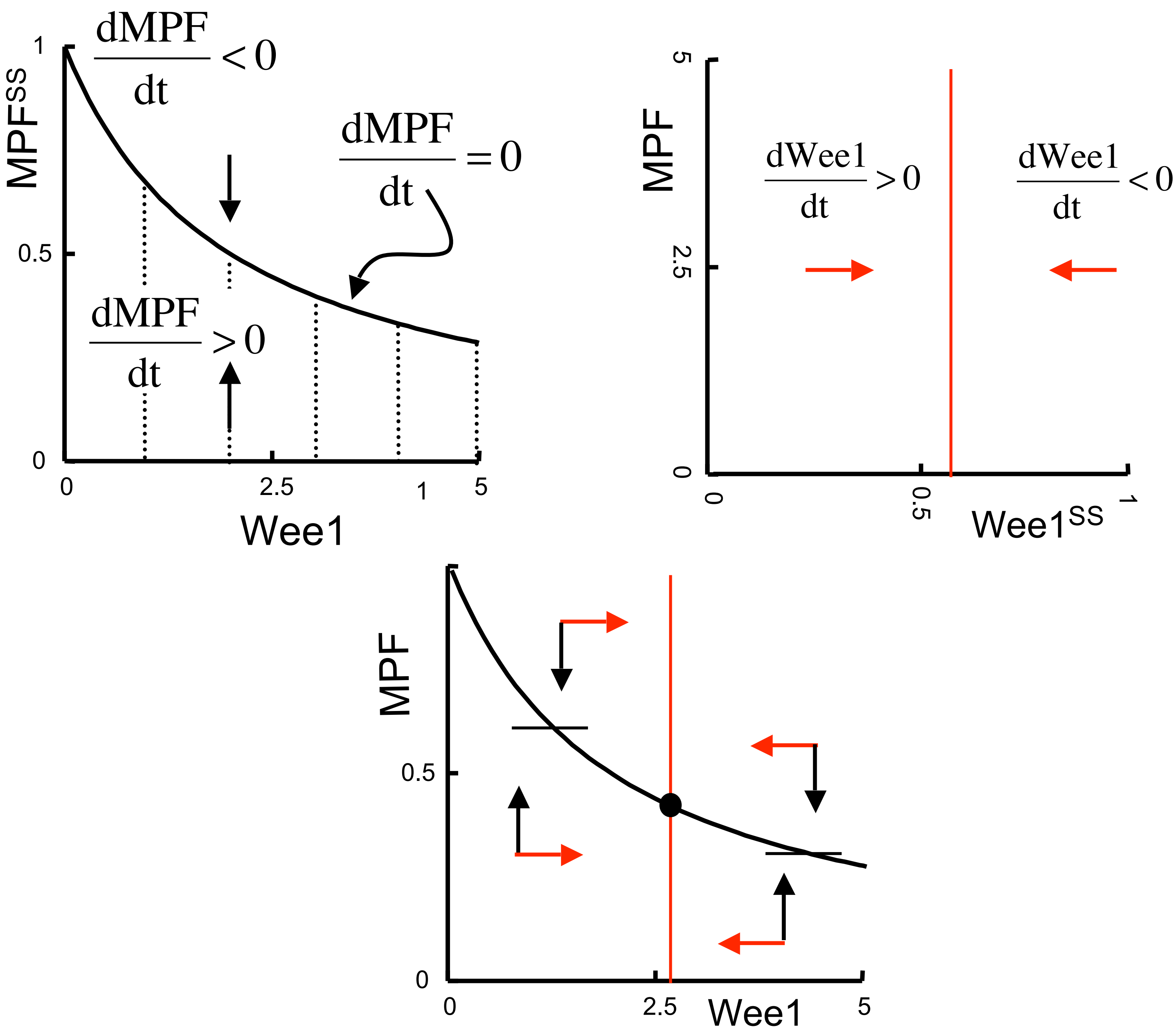


$$\frac{dMPF}{dt} = k_a \cdot (MPF_{tot} - MPF) - k_i \cdot MPF \cdot Wee1$$

$$\frac{dWee1}{dt} = \frac{k_{wa} \cdot (Wee1_{tot} - Wee1)}{J + Wee1_{tot} - Wee1} - \frac{k_{wi} \cdot Wee1}{J + Wee1}$$


MPF^{SS}
$\frac{dMPF}{dt} < 0$
$\frac{dMPF}{dt} = 0$
$\frac{dMPF}{dt} > 0$
1
0.5
0
0
1
2
2.5
3
4
5
Wee1

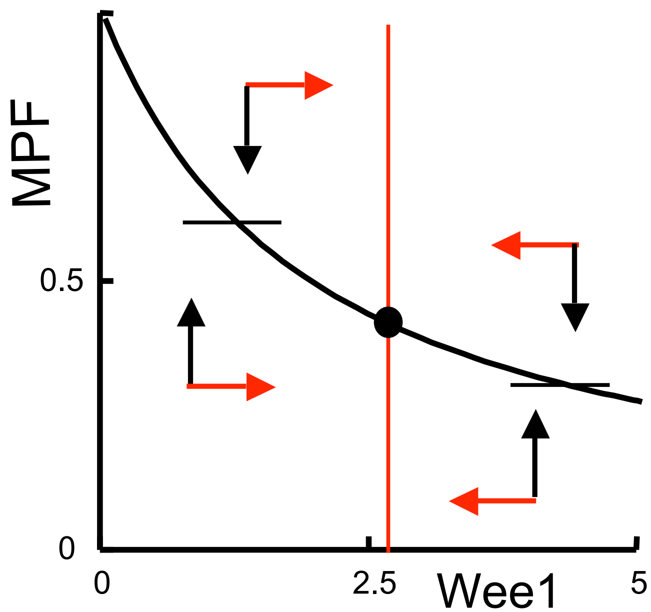

MPF
$\frac{dWee1}{dt} > 0$
$\frac{dWee1}{dt} < 0$
5
2.5
0
0
0.5
1
Wee1^{SS}

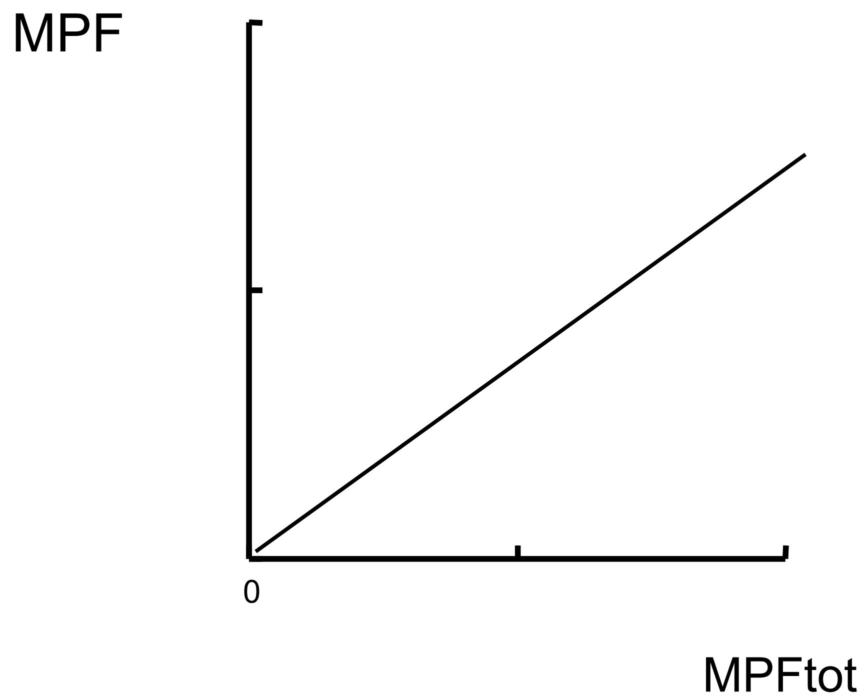


$\frac{dMPF}{dt} < 0$
$\frac{dMPF}{dt} = 0$
$\frac{dMPF}{dt} > 0$
MPFSS
1
0.5
0
0
2.5
1
5
Wee1
MPF
5
2.5
0
$\frac{dWee1}{dt} > 0$
$\frac{dWee1}{dt} < 0$
0
0.5
1
Wee1SS
MPF
0.5
0
0
2.5
Wee1
5

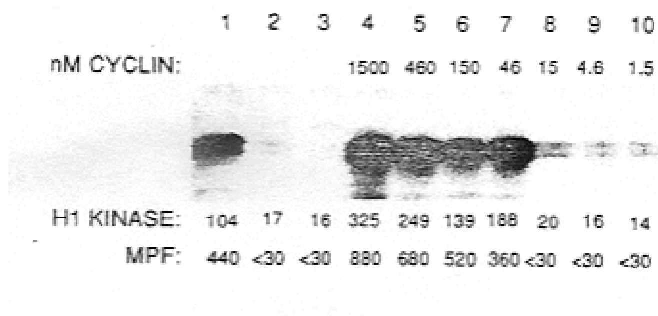
How does MPF increases with Cyclin total?

$$MPF^{SS} = \frac{k_a \cdot MPF_{tot}}{k_i \cdot Wee1 + k_a}$$

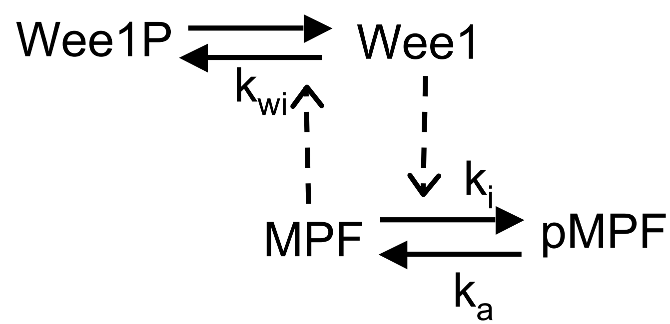




Not quite the same!

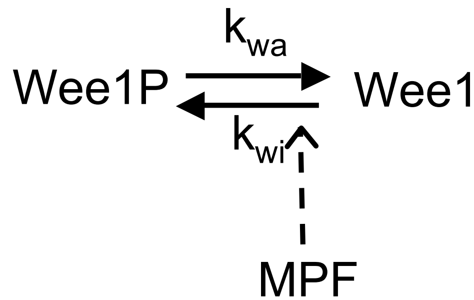


Solomon et al, Cell, 1990



Wee1P
Wee1
k_wi
k_i
MPF
pMPF
k_a

Michaelis-Menten: catalyzed reversible reaction

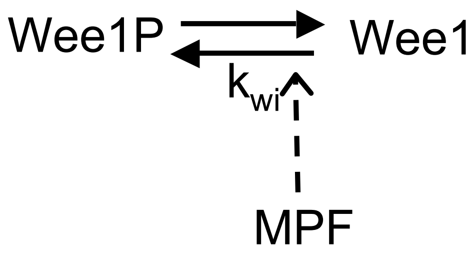


$$\frac{dWee1}{dt} = \frac{k_{wa} \cdot (Wee1_{tot} - Wee1)}{J + Wee1_{tot} - Wee1} - \frac{k_{wi} \cdot Wee1 \cdot MPF}{J + Wee1}$$

production
+

elimination
-

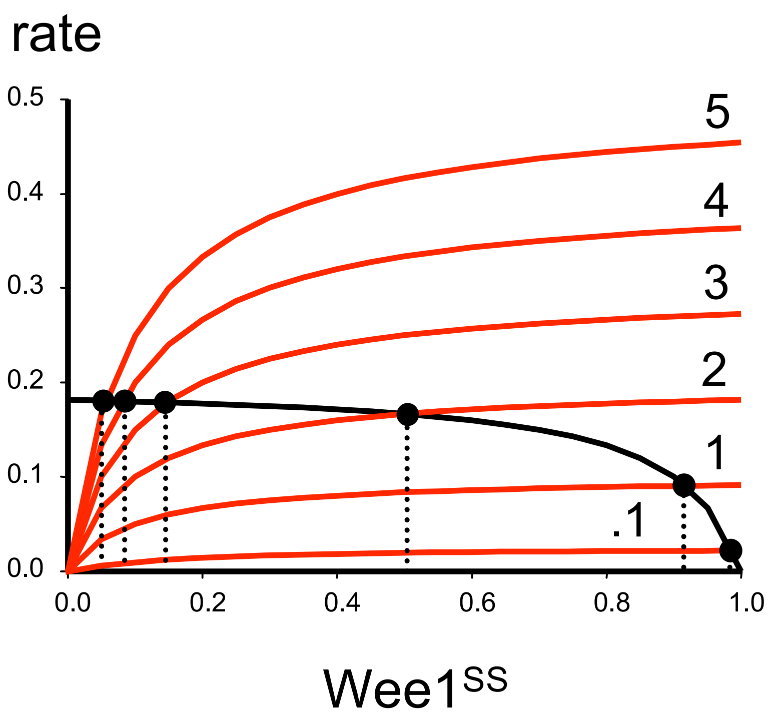
Nullclines

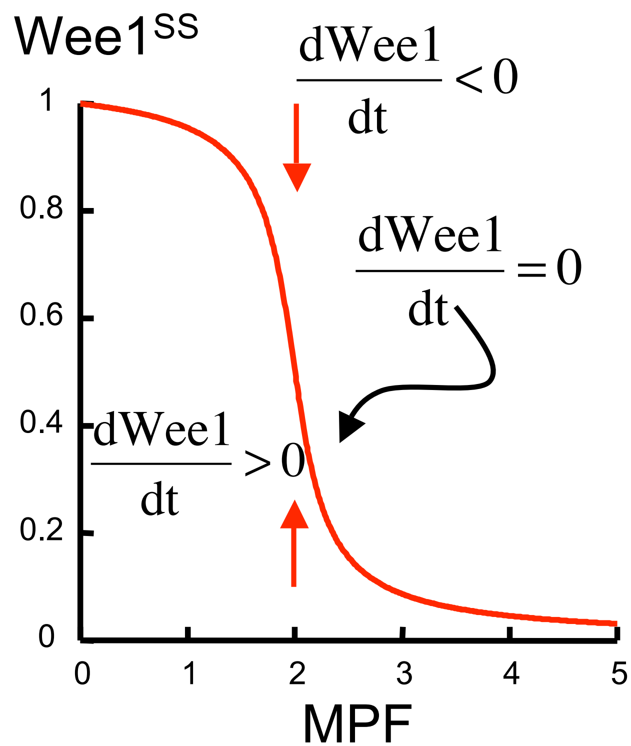


$$\frac{dWee1}{dt} = \underbrace{\frac{k_{wa} \cdot (Wee1_{tot} - Wee1)}{J + Wee1_{tot} - Wee1}}_{\text{production } +} - \underbrace{\frac{k_{wi} \cdot Wee1 \cdot MPF}{J + Wee1}}_{\text{elimination } -}$$

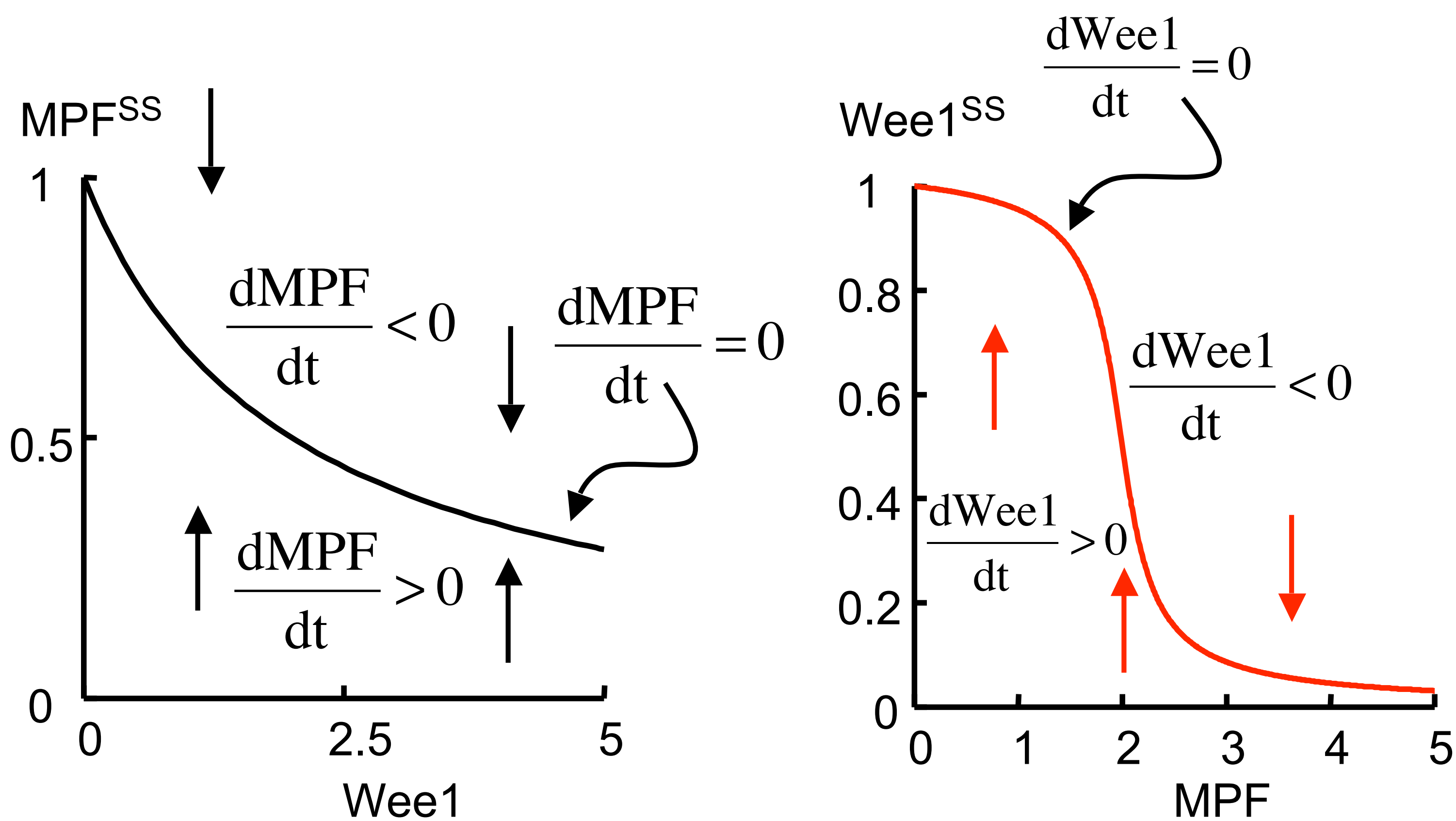
production
+

elimination
-

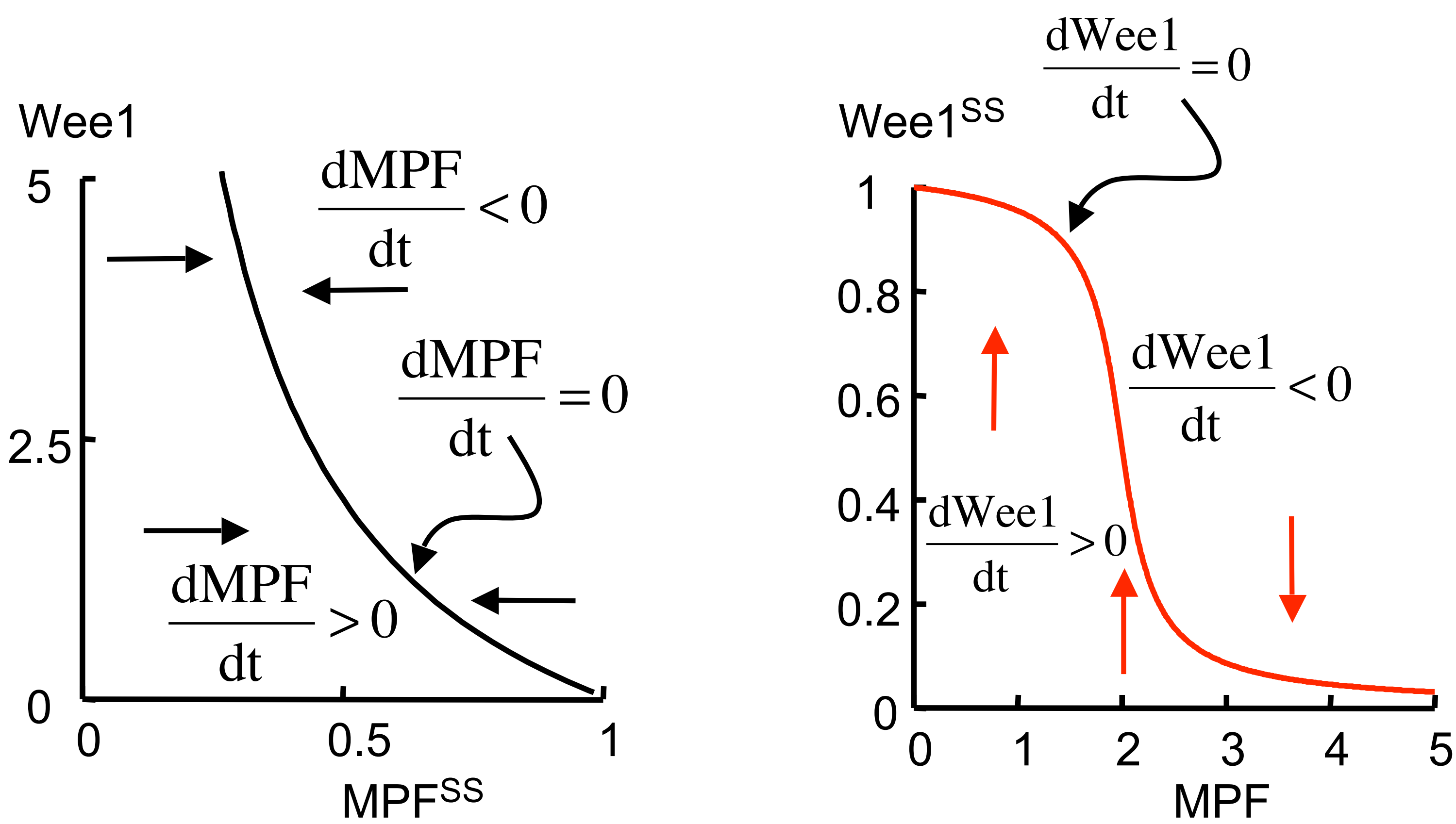




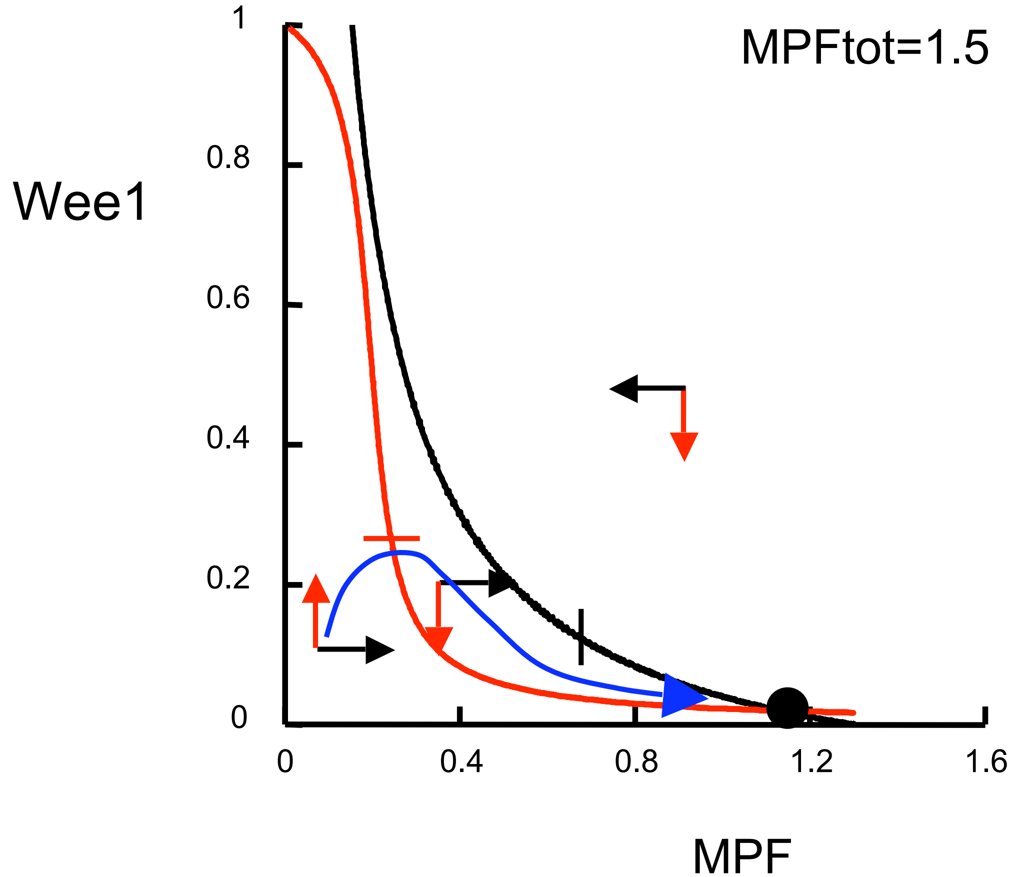
Phase plane analysis



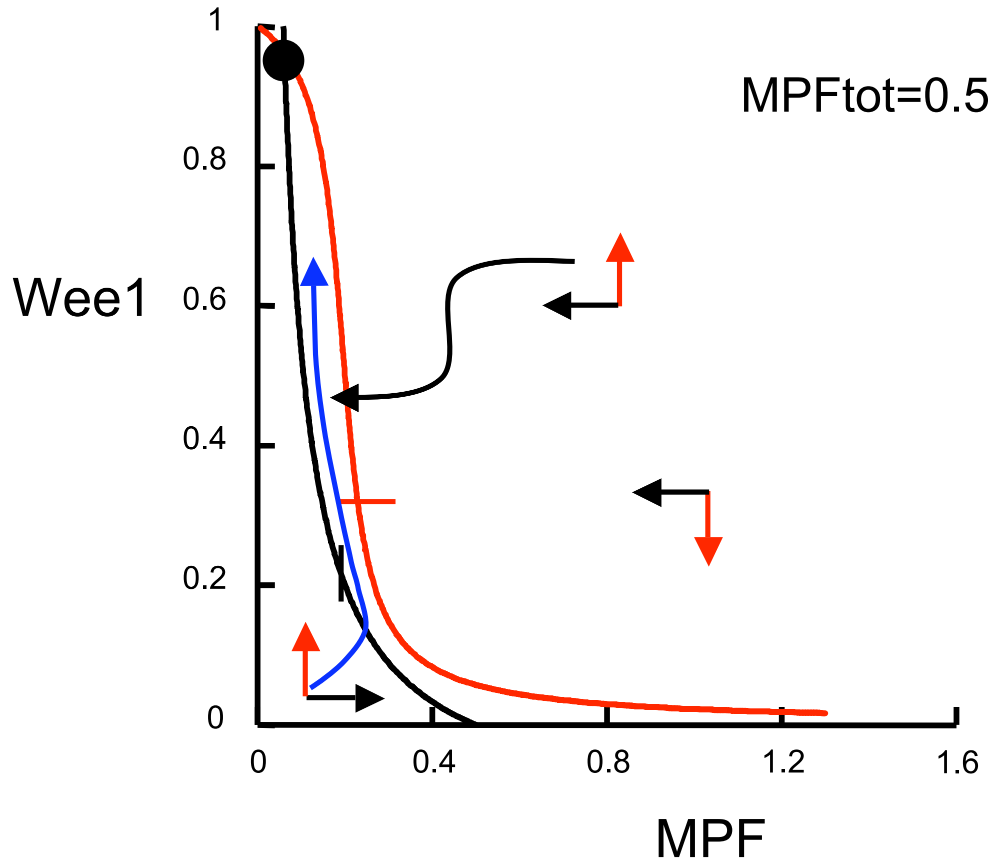
Phase plane analysis



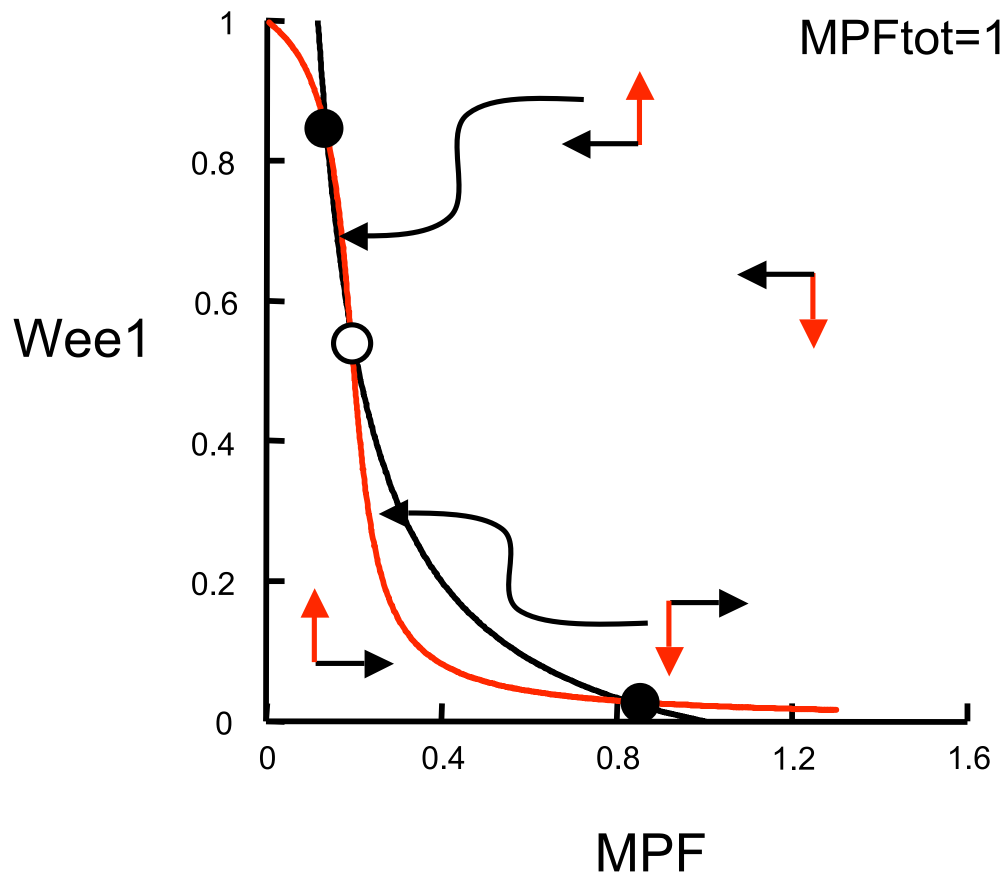
First solution, MPF wins, Wee1 loses



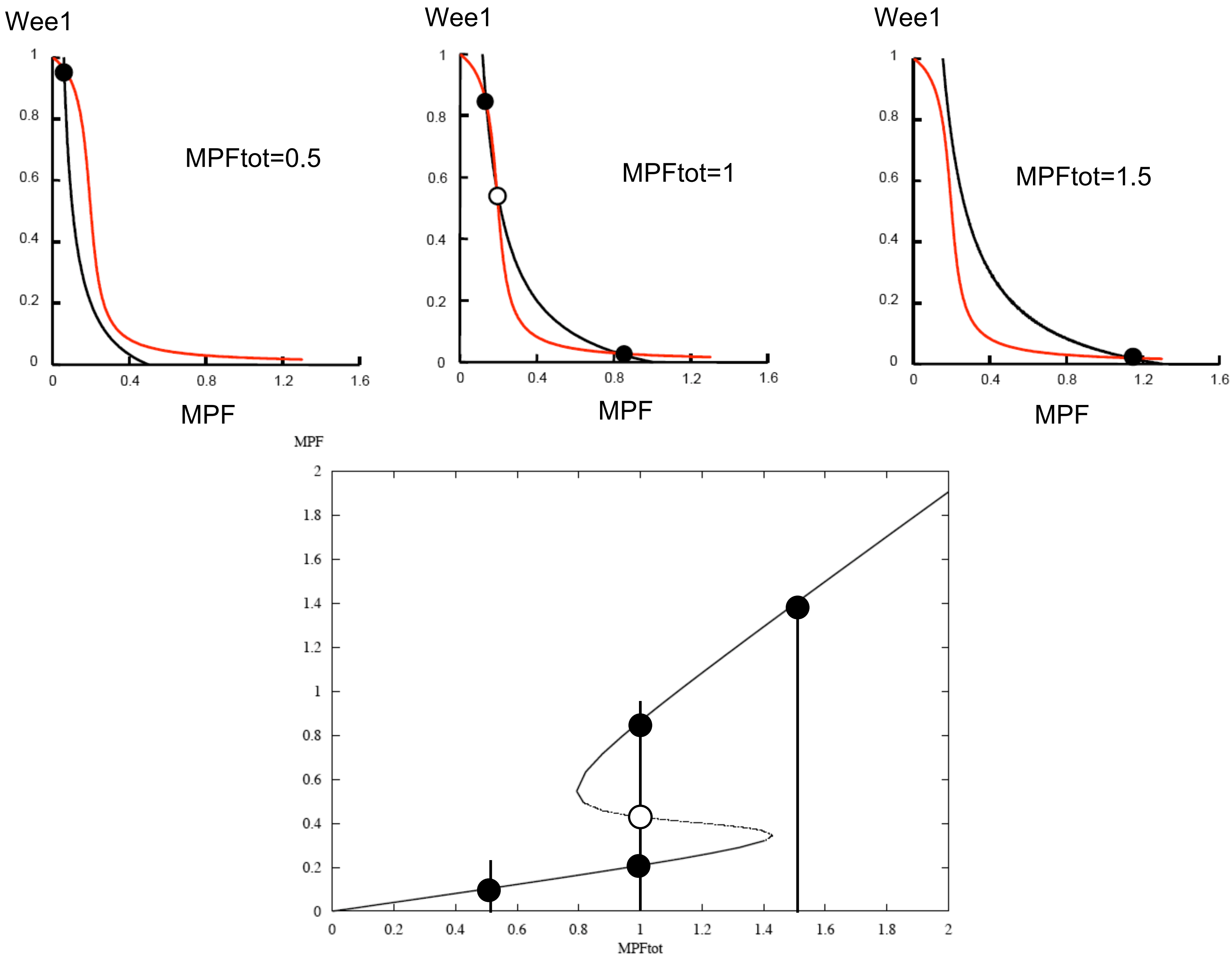
Second solution, Wee1 wins, MPF loses



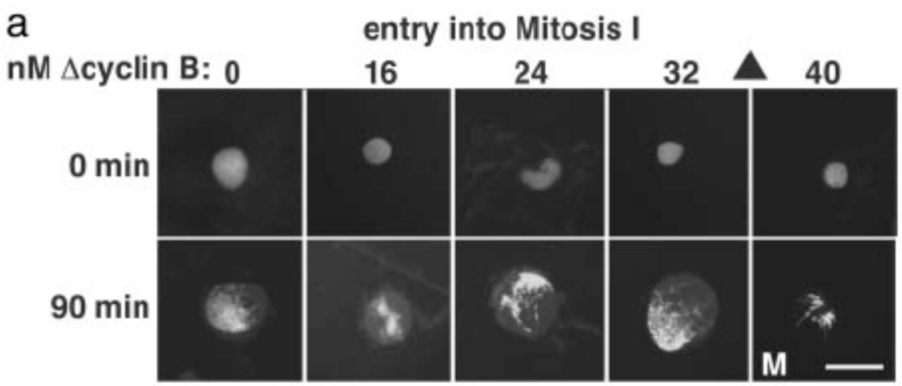
Third solution, both can win: hysteresis

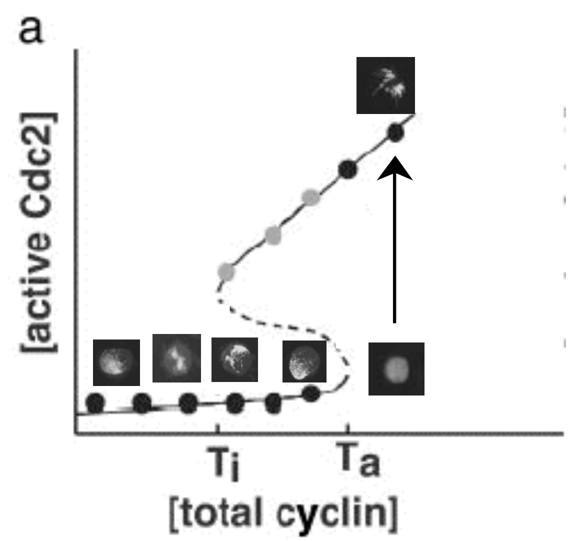


How does MPF increases with Cyclin total?


Wee1
MPFtot=0.5
MPF
Wee1
MPFtot=1
MPF
Wee1
MPFtot=1.5
MPF
MPF
MPFtot

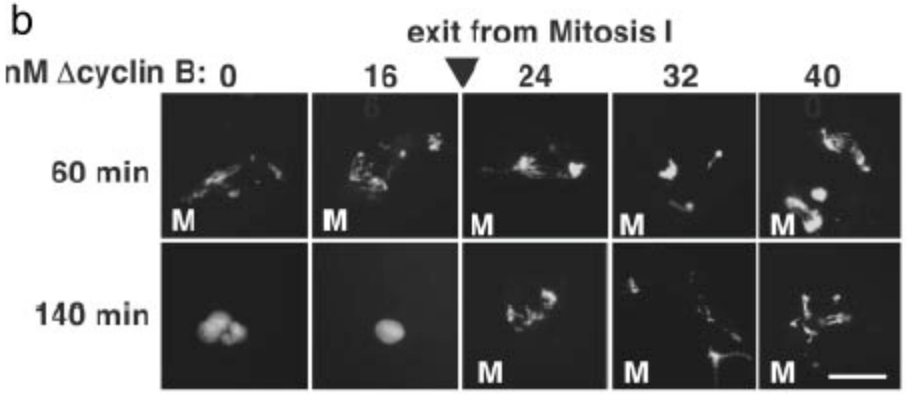
Hysteresis in the Xenopus early cycles: simulation of an experimental result





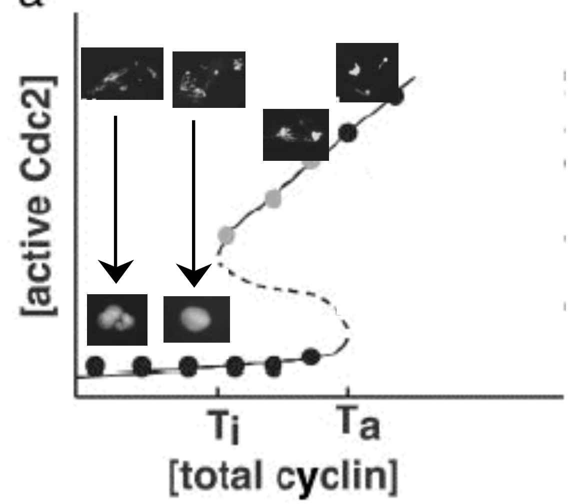
From Sha et al, PNAS, 2003

b



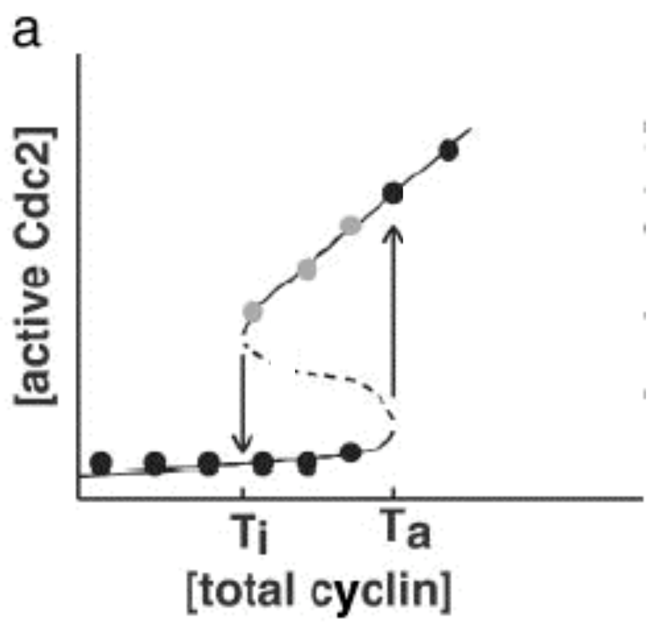
exit from Mitosis I
nM Δcyclin B: 0
16
24
32
40
60 min
140 min
M

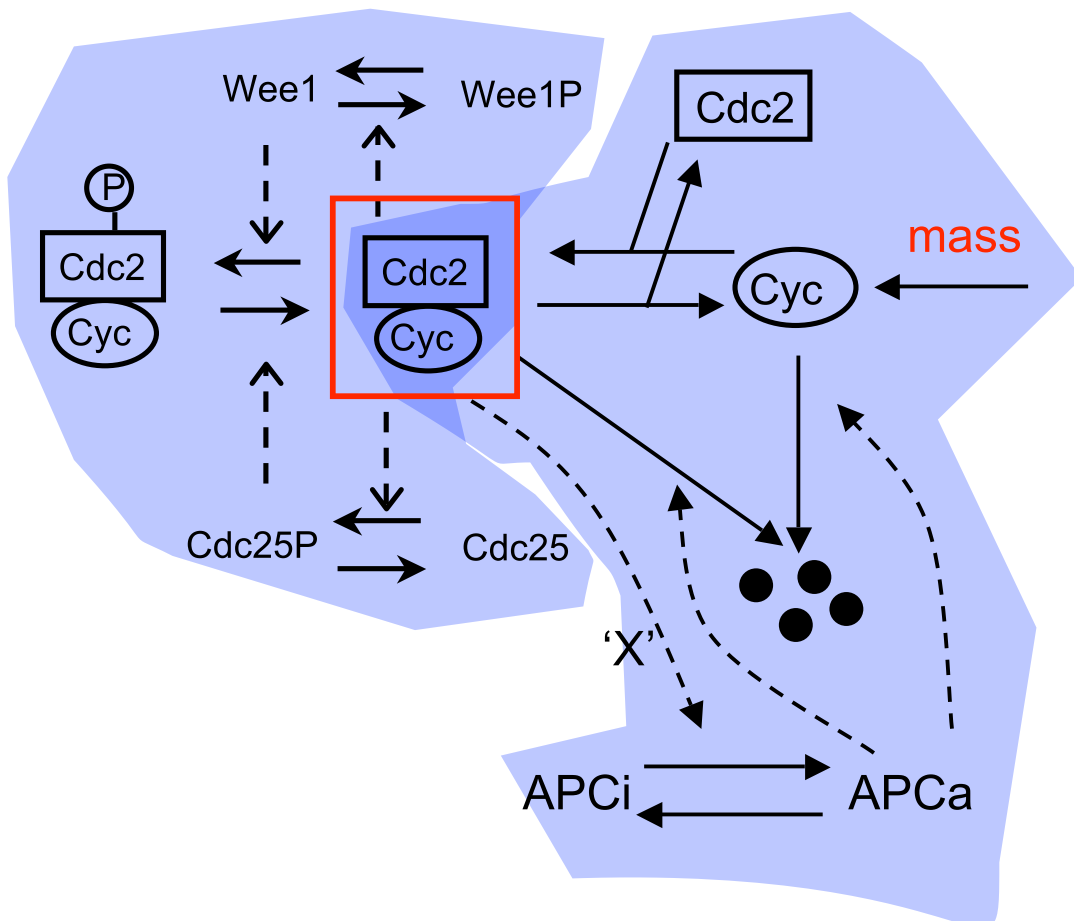
a



[active Cdc2]
Ti
Ta
[total cyclin]

What happens if cyclin total increases with cell mass?

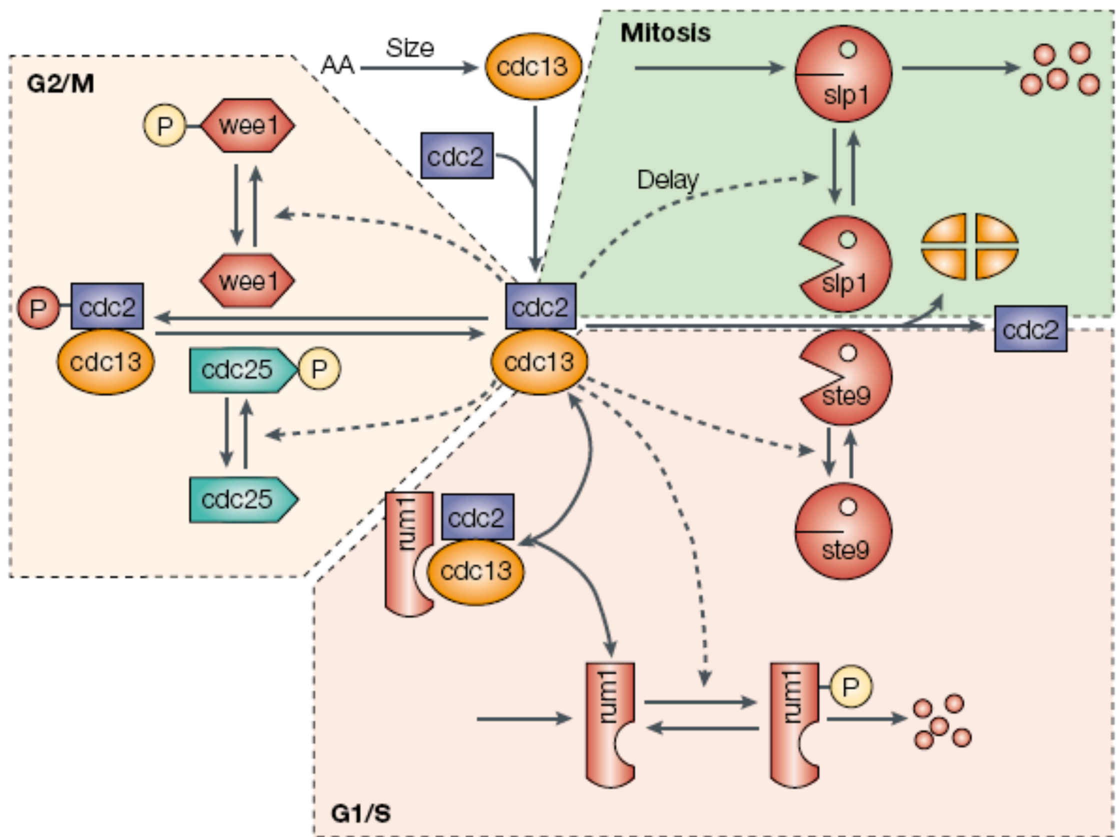


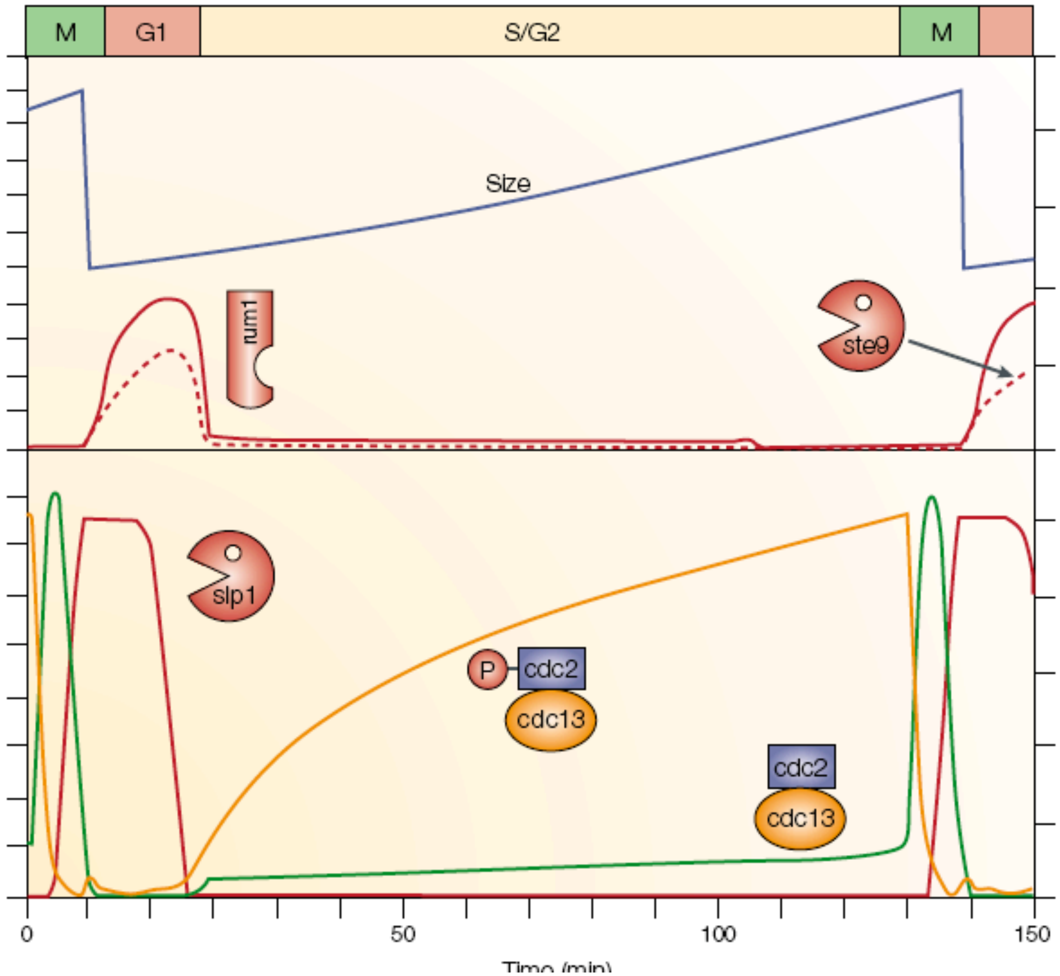

Wee1
Wee1P
Cdc2
P
Cdc2
Cyc
Cdc2
Cyc
Cyc
mass
Cdc25P
Cdc25
'X'
APCi
APCa

NETWORK DYNAMICS AND CELL PHYSIOLOGY

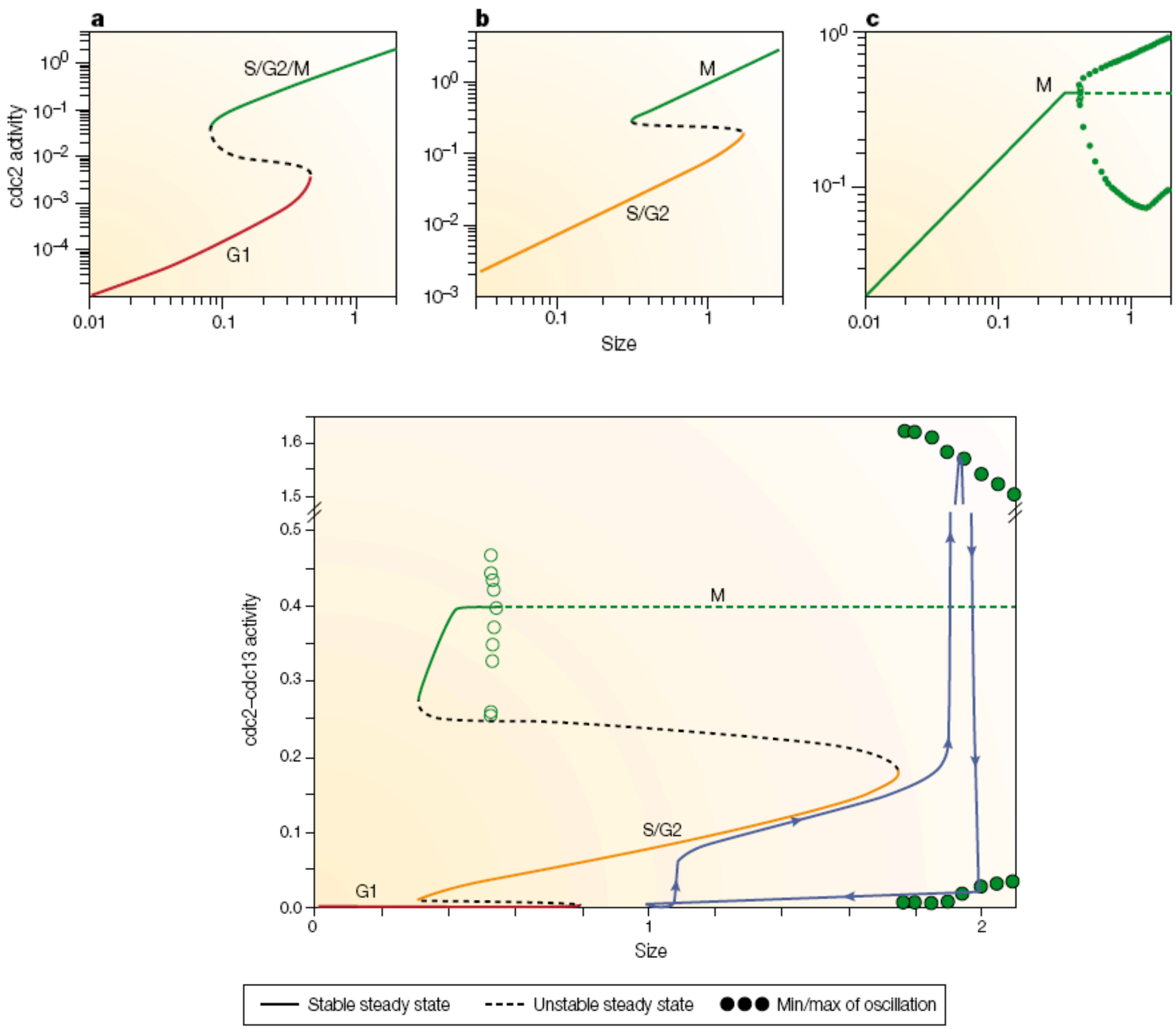
John J. Tyson, Kathy Chen* and Bela Novak‡*

NATURE REVIEWS | MOLECULAR CELL BIOLOGY DECEMBER 2001 | VOLUME 2





M
G1
S/G2
M
Size
rum1
ste9
slp1
P
cdc2
cdc13
cdc2
cdc13
0
50
100
150



a
b
c
cdc2 activity
S/G2/M
G1
M
S/G2
Size
cdc2–cdc13 activity
Stable steady state
Unstable steady state
Min/max of oscillation

Conclusion

-Same wiring in different organisms, combination of positive and negative feedbacks.

- In Xenopus early development, with large mass, the cell cycle is a limit cycle oscillator, the negative feedback plays the key role.
- Artificially, an additional mechanism of control emerges, based on a positive feedback loop.
- Both positive and negative feedbacks are at work in yeast. In these organisms, mass growth drives the cell cycle.
- Positive feedbacks introduce checkpoints and irreversibility in the cycle. The negative feedback the capability to start a new process.

Can a biologist fix a radio?—Or, what I learned while studying apoptosis

CANCER CELL : SEPTEMBER 2002

Yuri Lazebnik

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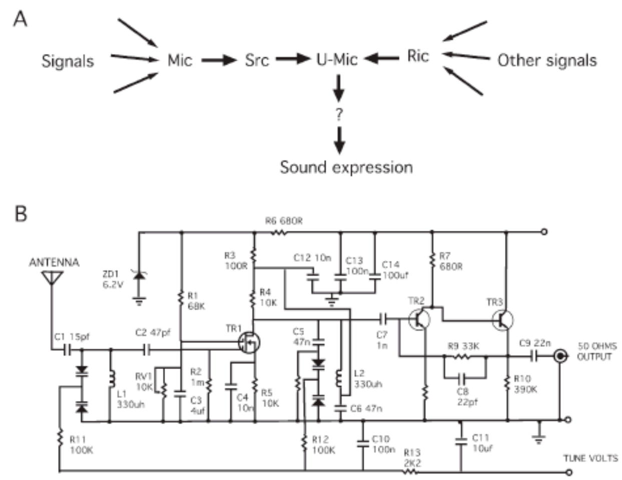

Figure 3. The tools used by biologists and engineers to describe processes of interest

A: The biologist's view of a radio. See Figure 2 and text for description of the indicated components. **B:** The engineer's view of a radio. (Please note that the circuit diagram presented is not that of the radio used in the study. The diagram of the radio was lost, which, in part, explains why the radio remains broken.)