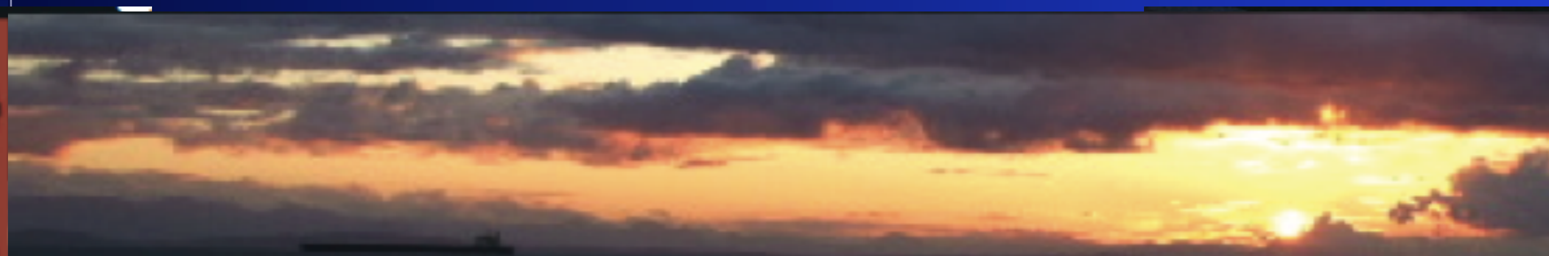
Mathematical Cell Biology Graduate Summer Course

University of British Columbia, May 1-31, 2012

Leah Edelstein-Keshet

Switches, Oscillators, and the Cell Cycle



mprime

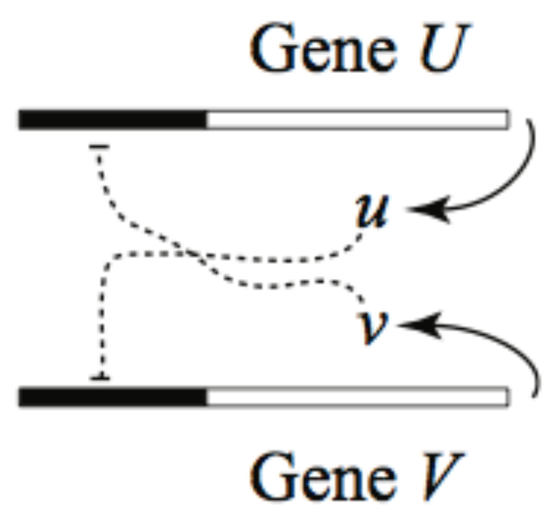
PIMS

www.math.ubc.ca/~keshet/MCB2012/

What to notice so far

- There are two ways to design a regulatory cell network:
- (1) protein-protein interactions (mutual phosphorylation, etc etc) (time scale: sec-min)
- (2) gene networks (time scale: hrs day)

Gene circuits

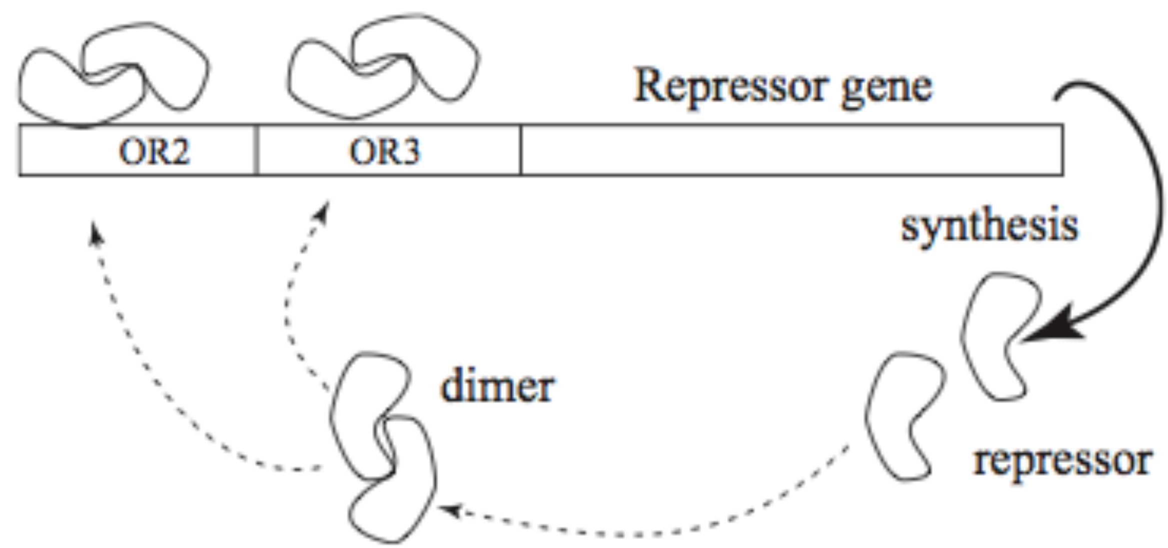


Construction of a genetic toggle switch in *Escherichia coli*

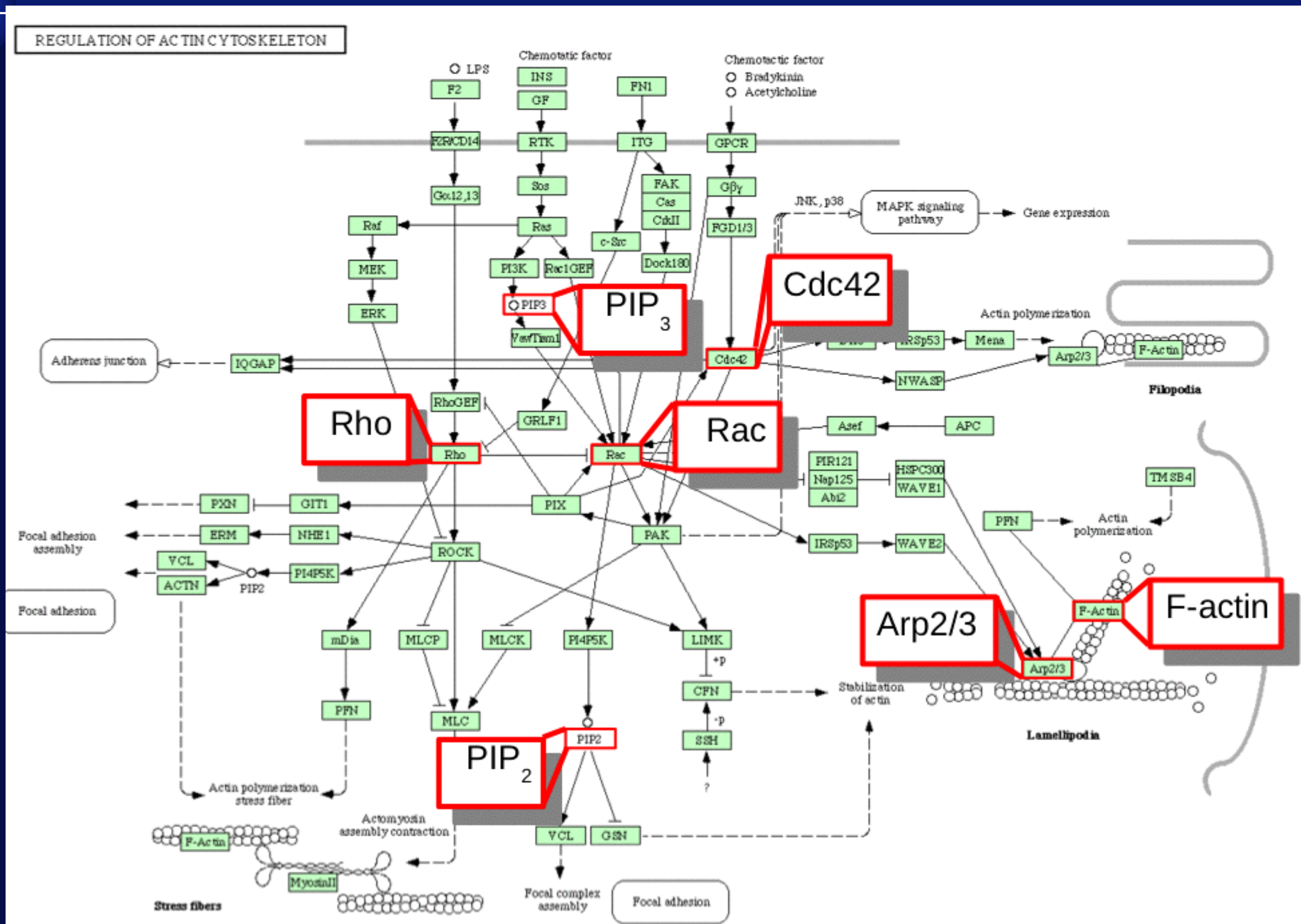
Timothy S. Gardner*†, Charles R. Cantor* & James J. Collins*†

Noise-based switches and amplifiers for gene expression

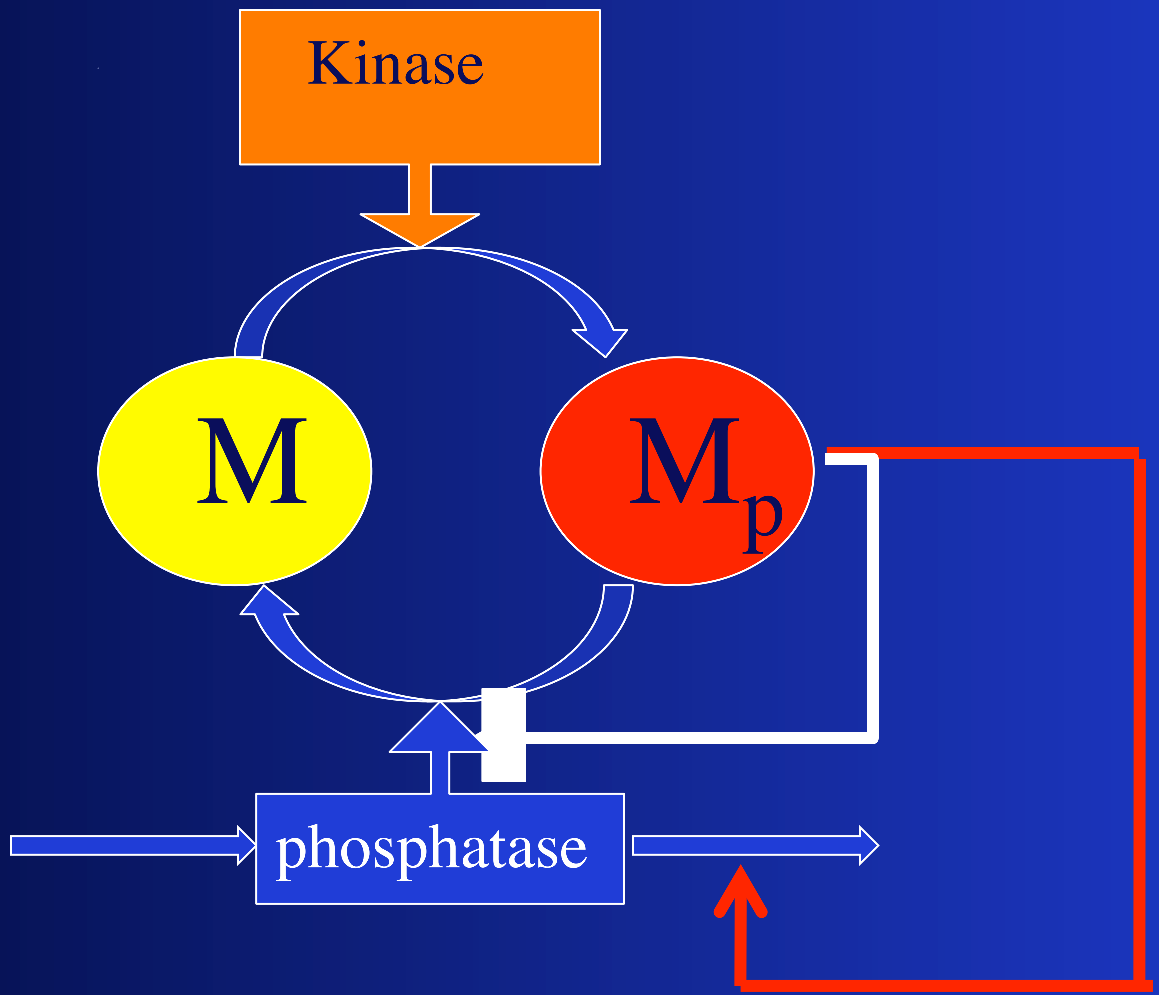
Jeff Hasty*†, Joel Pradines*, Milos Dolnik*‡, and J. J. Collins*



Protein circuits



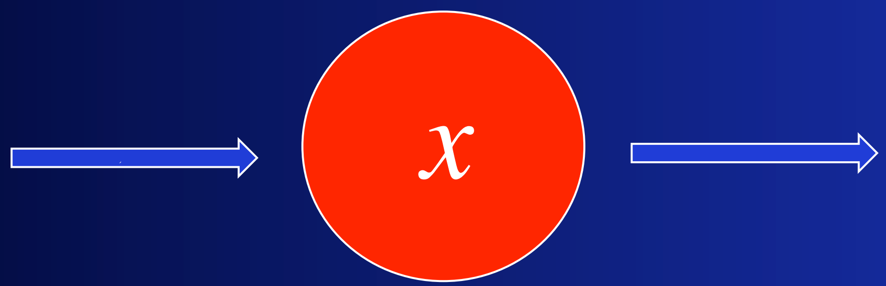
Protein circuits



Other things to notice

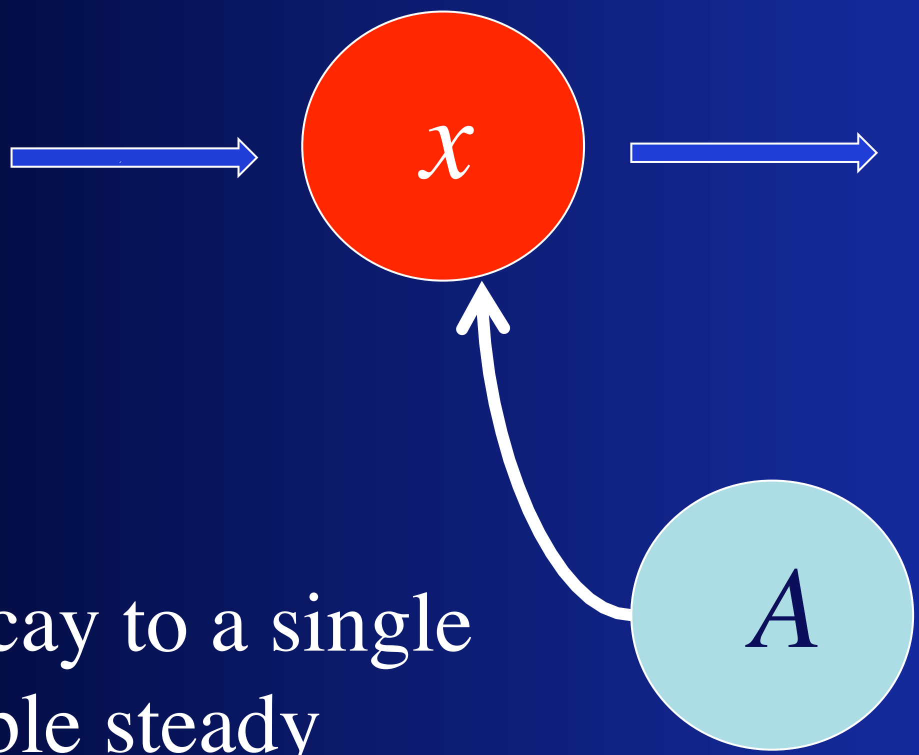
- By building up feedback interactions it is possible to obtain new dynamics :
- (1) Simple decay to steady state
- (2) Switch (bistability)
- (3) Oscillator (stable cycles)

No feedback



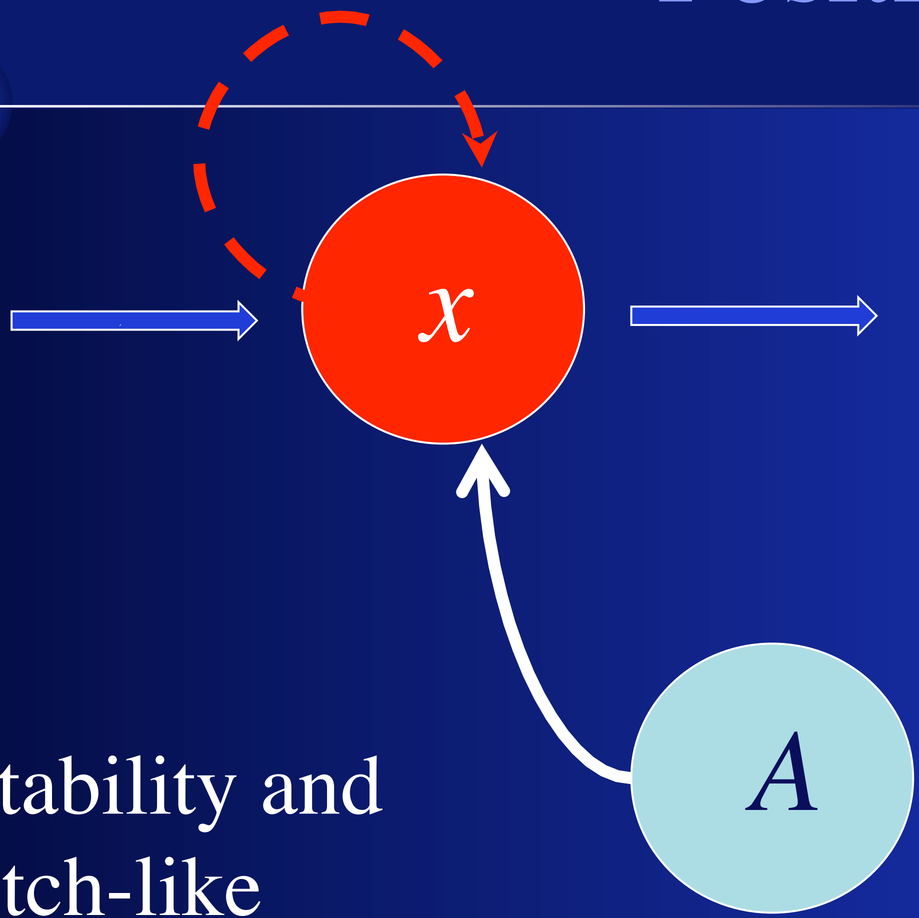
Decay to a single stable steady state

No feedback



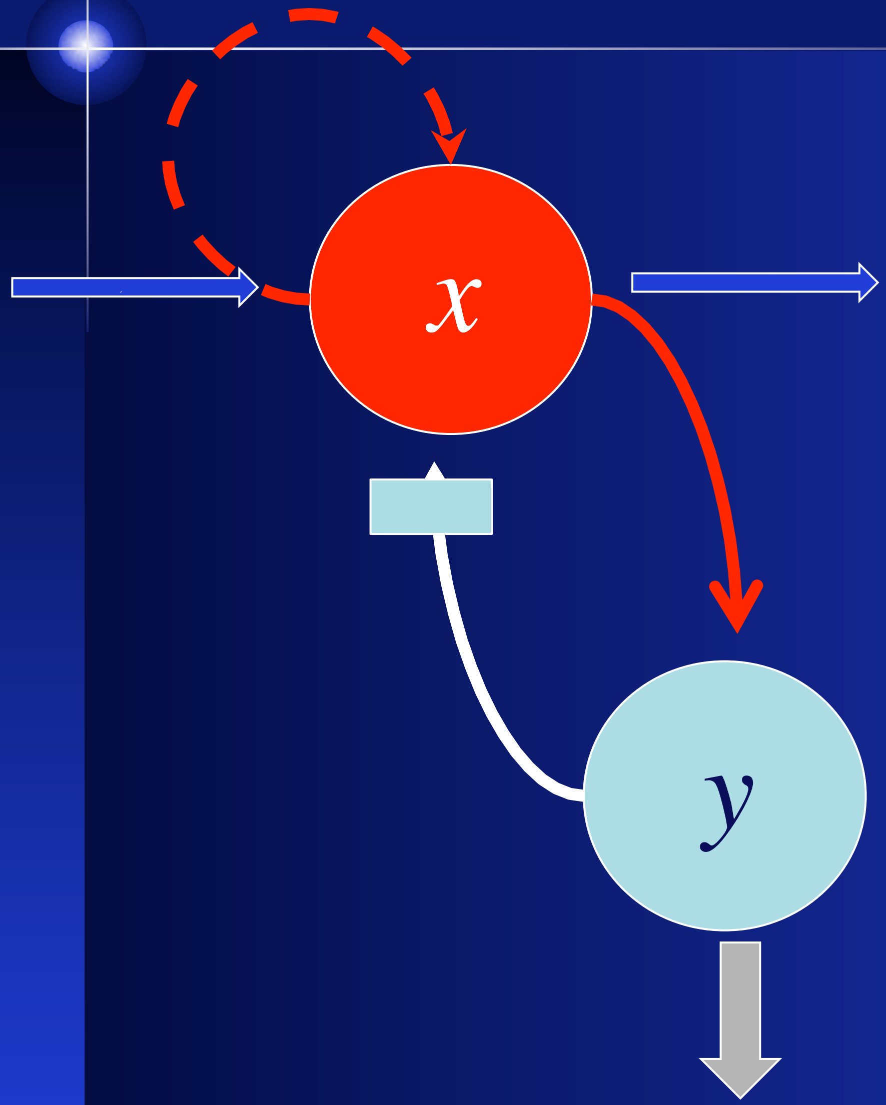
Decay to a single stable steady state

Positive feedback



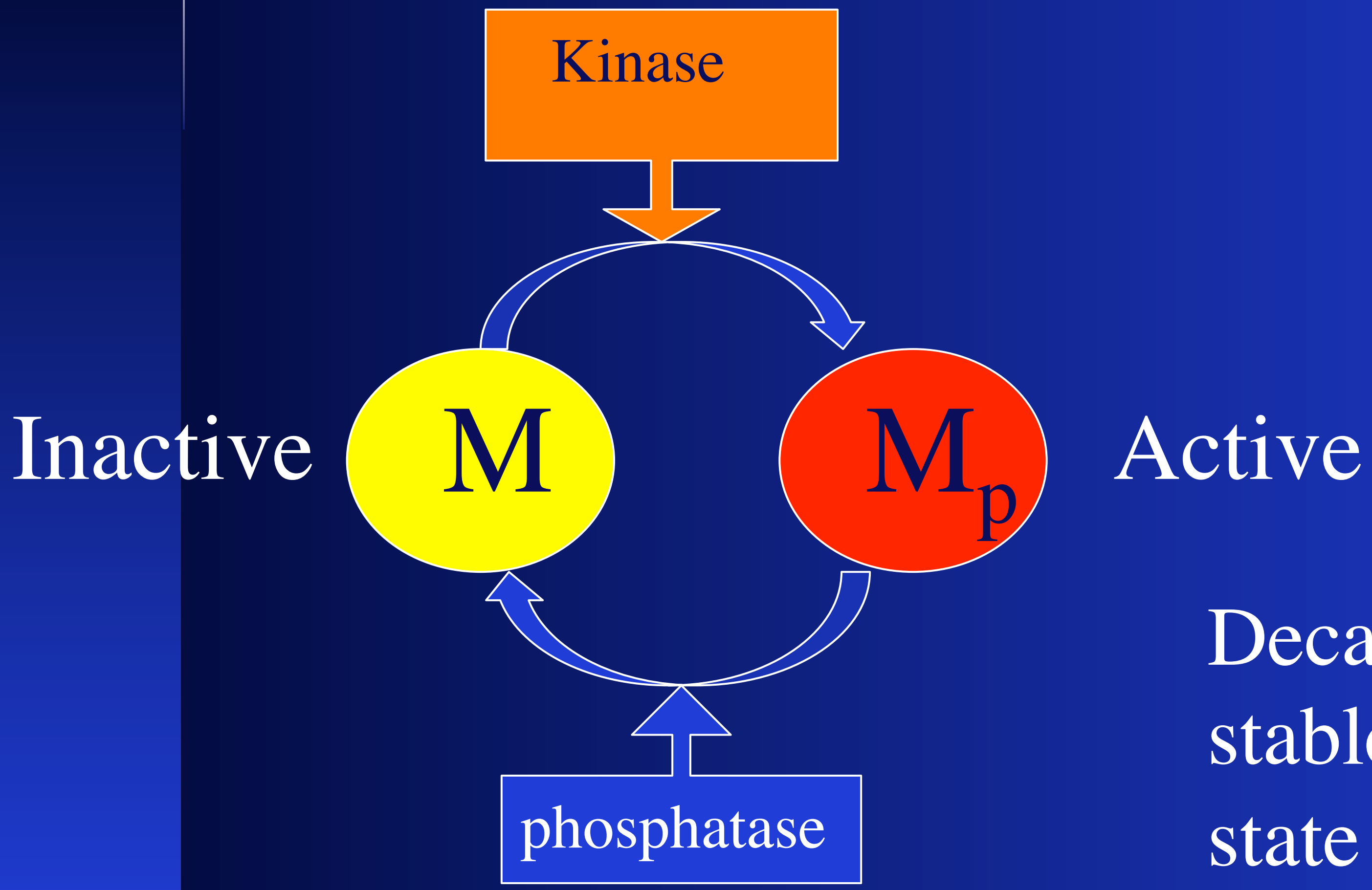
Bistability and switch-like behaviour possible

Add negative feedback



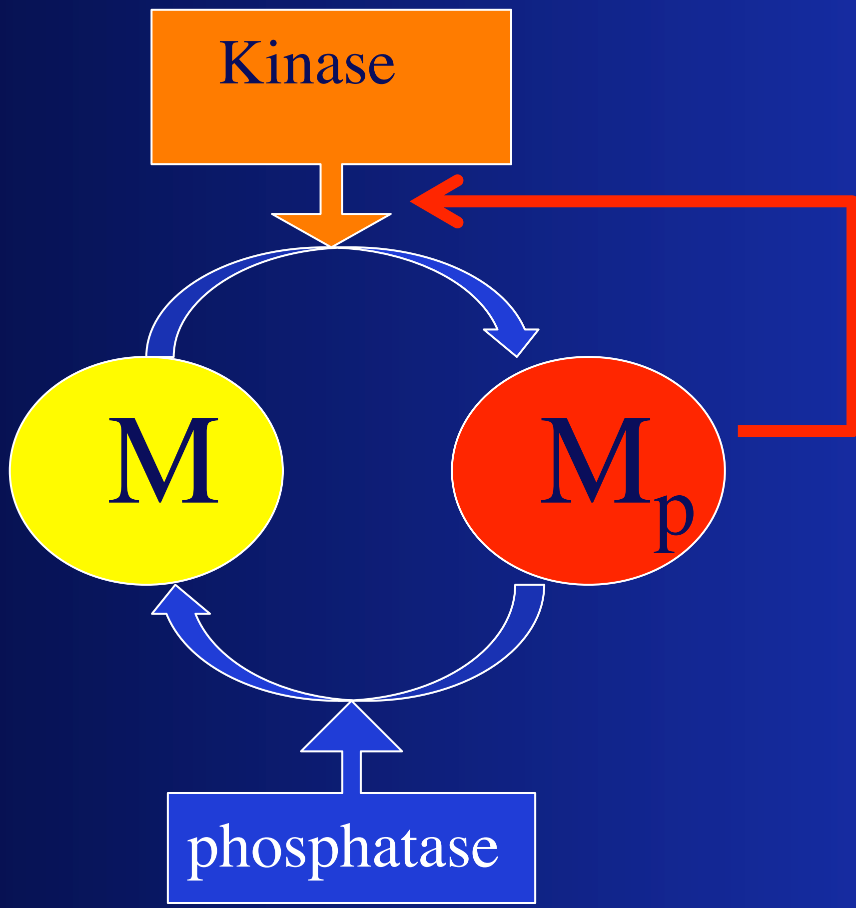
Stable cycles possible

Example: Phosphorylation cycle



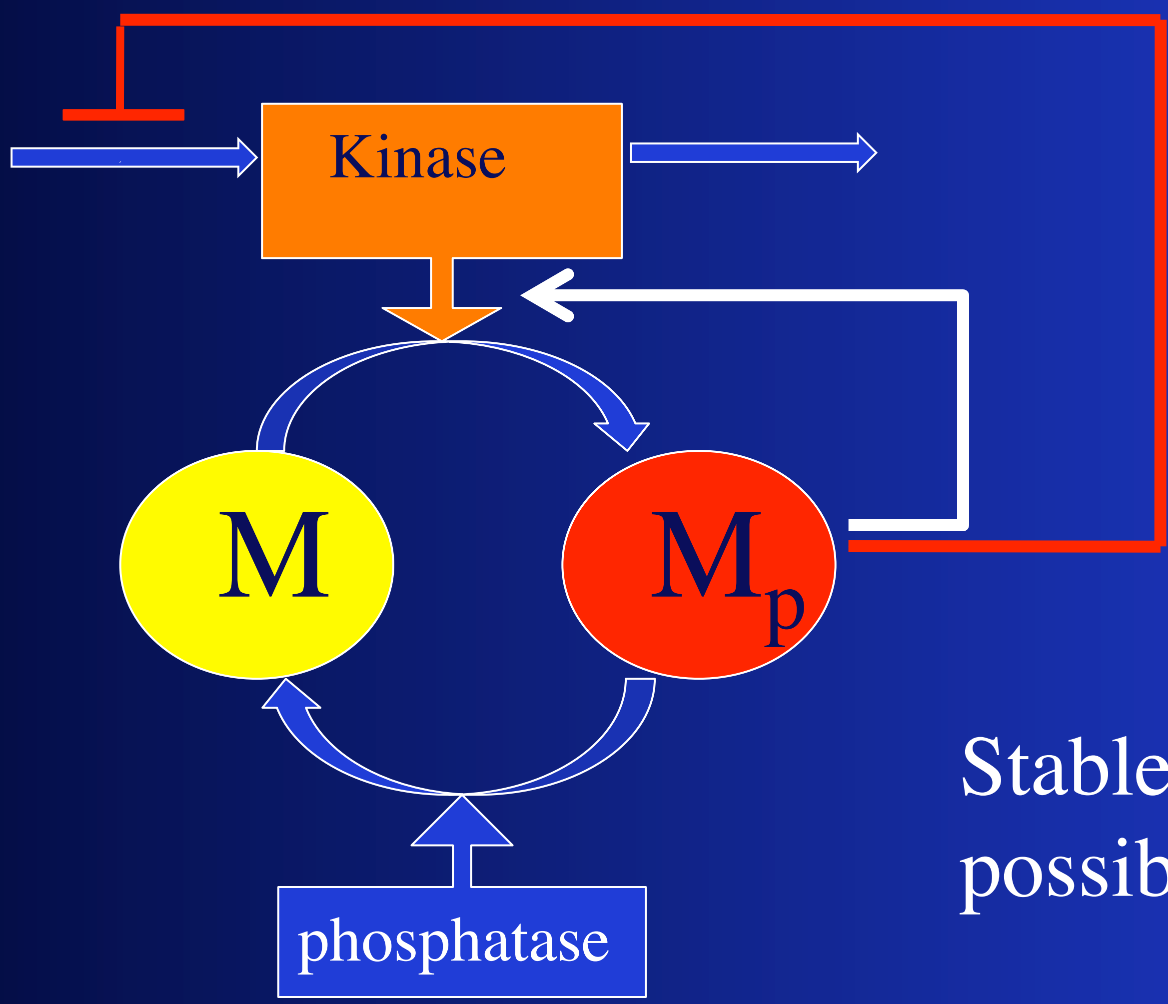
Decay to a single stable steady state

Add positive feedback to kinase



Bistability and switch-like behaviour possible

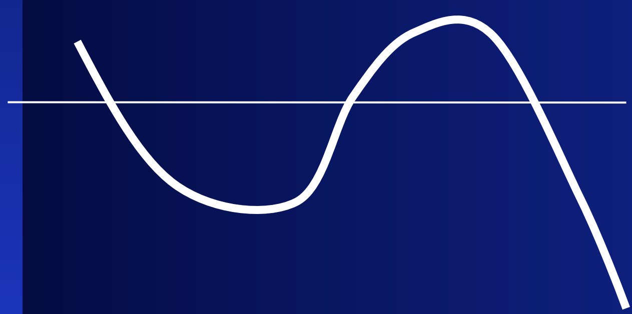
Add further negative feedback

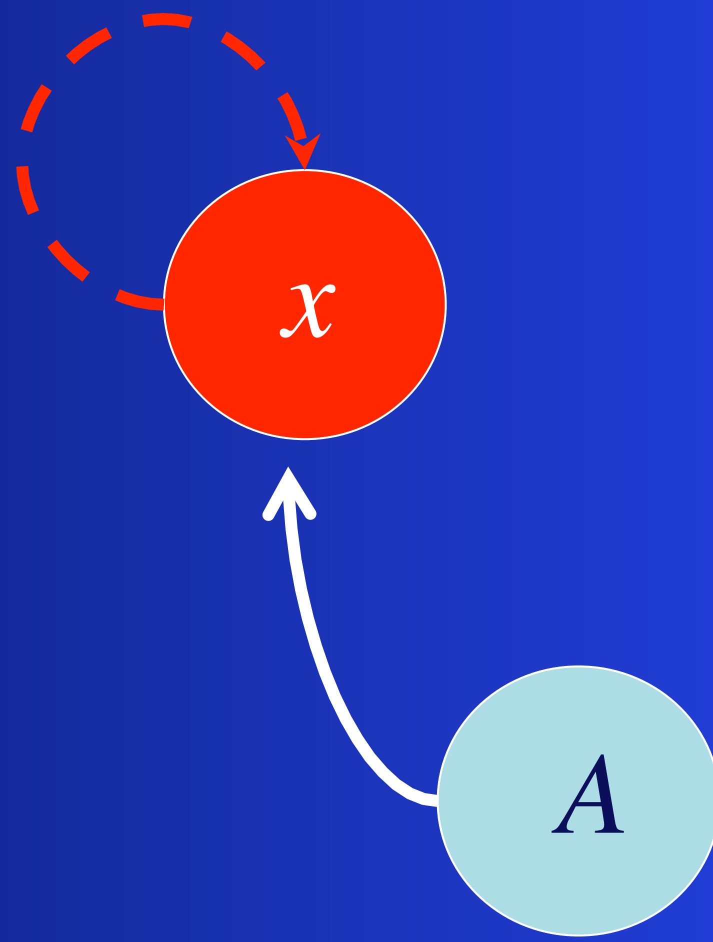


Stable cycles possible

Simple mathematical example

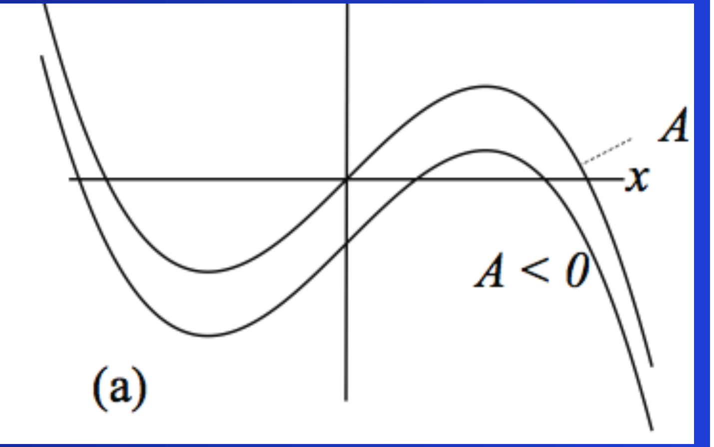
$$\frac{dx}{dt} = c\left(x - \frac{1}{3}x^3 + A\right)$$

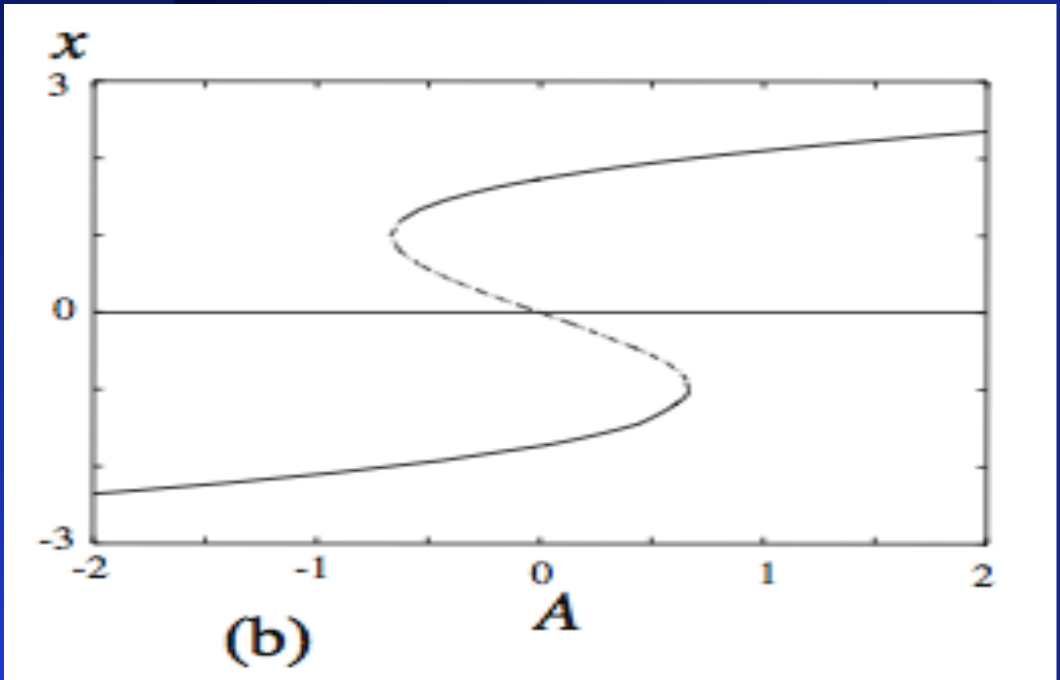




A switch (Generic bistability)

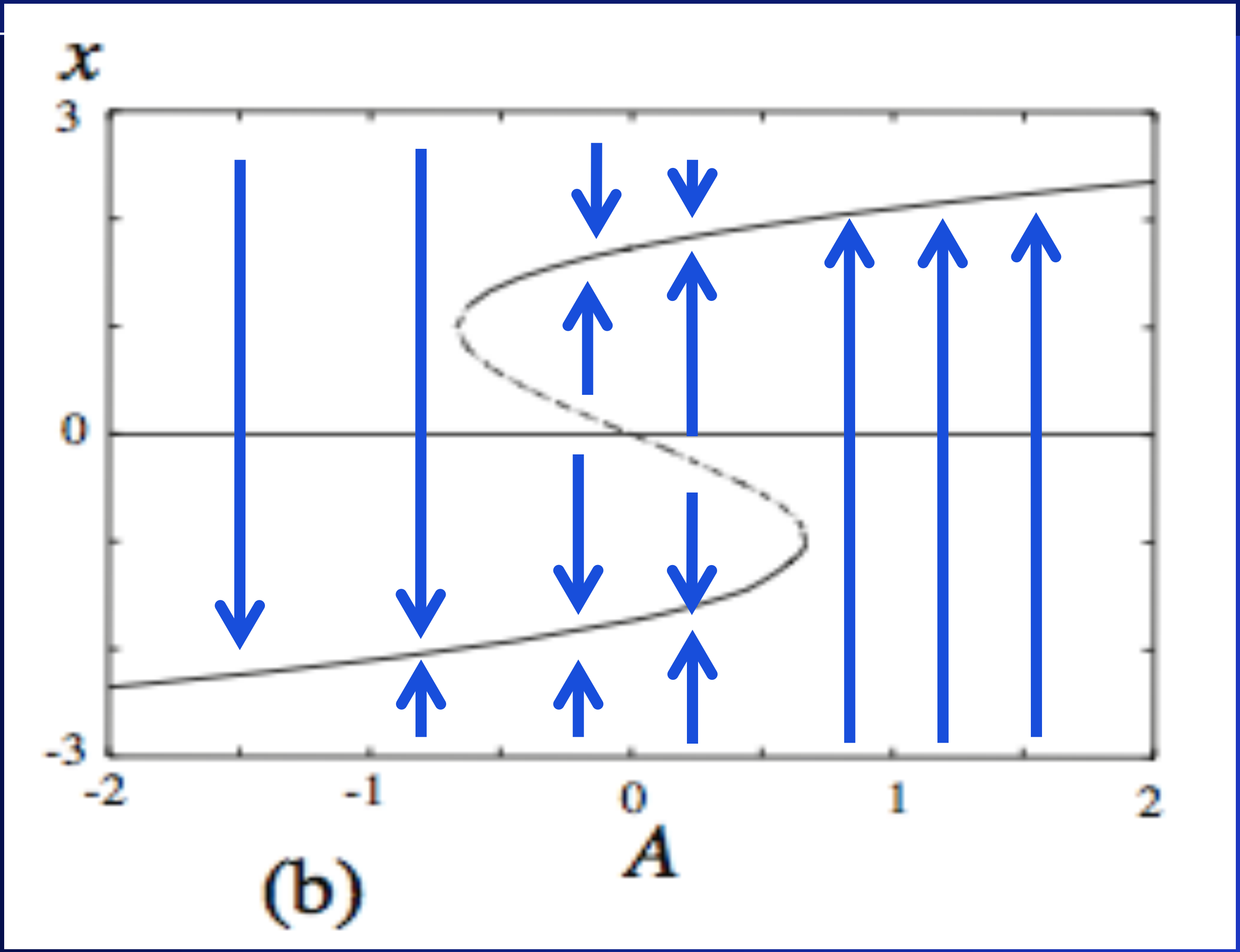
$$\frac{dx}{dt} = c\left(x - \frac{1}{3}x^3 + A\right)$$





The parameter A controls the switch

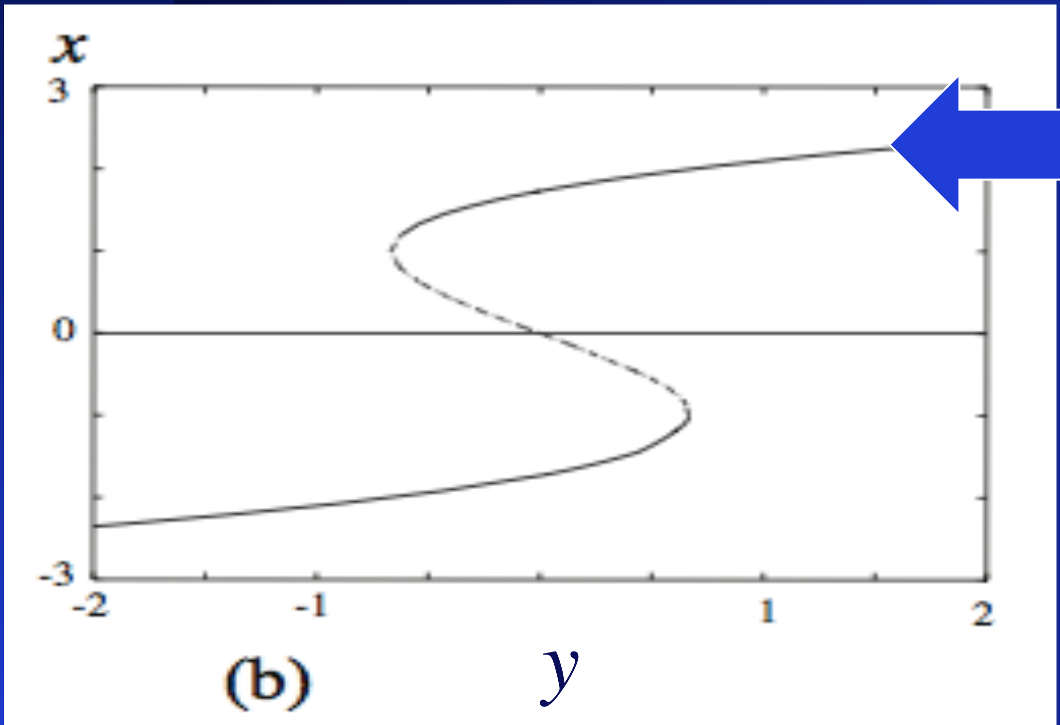
A controls the switch



"Switch" (Generic bistability)

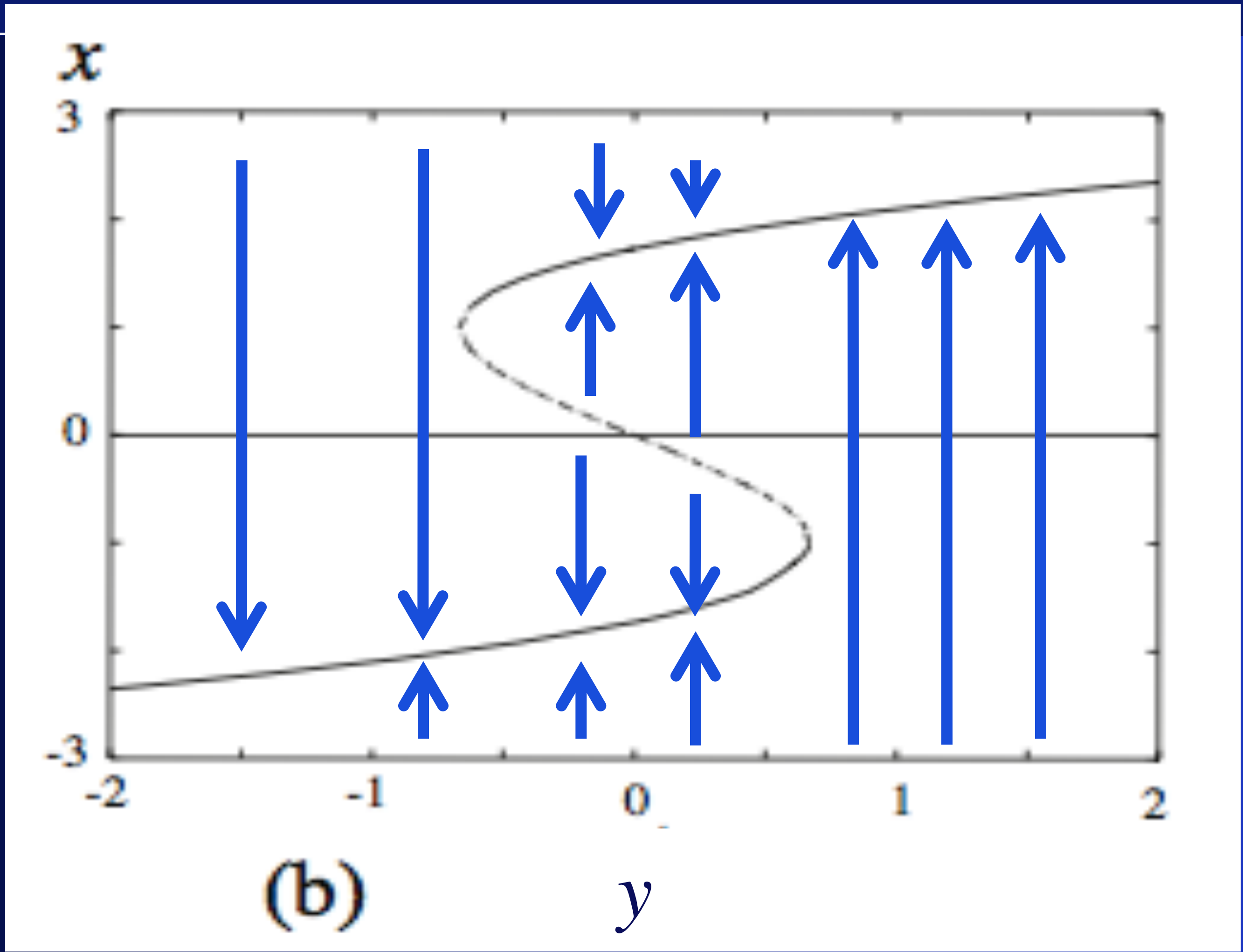
$$\frac{dx}{dt} = c\left(x - \frac{1}{3}x^3 + y\right)$$

The "parameter" y controls the switch

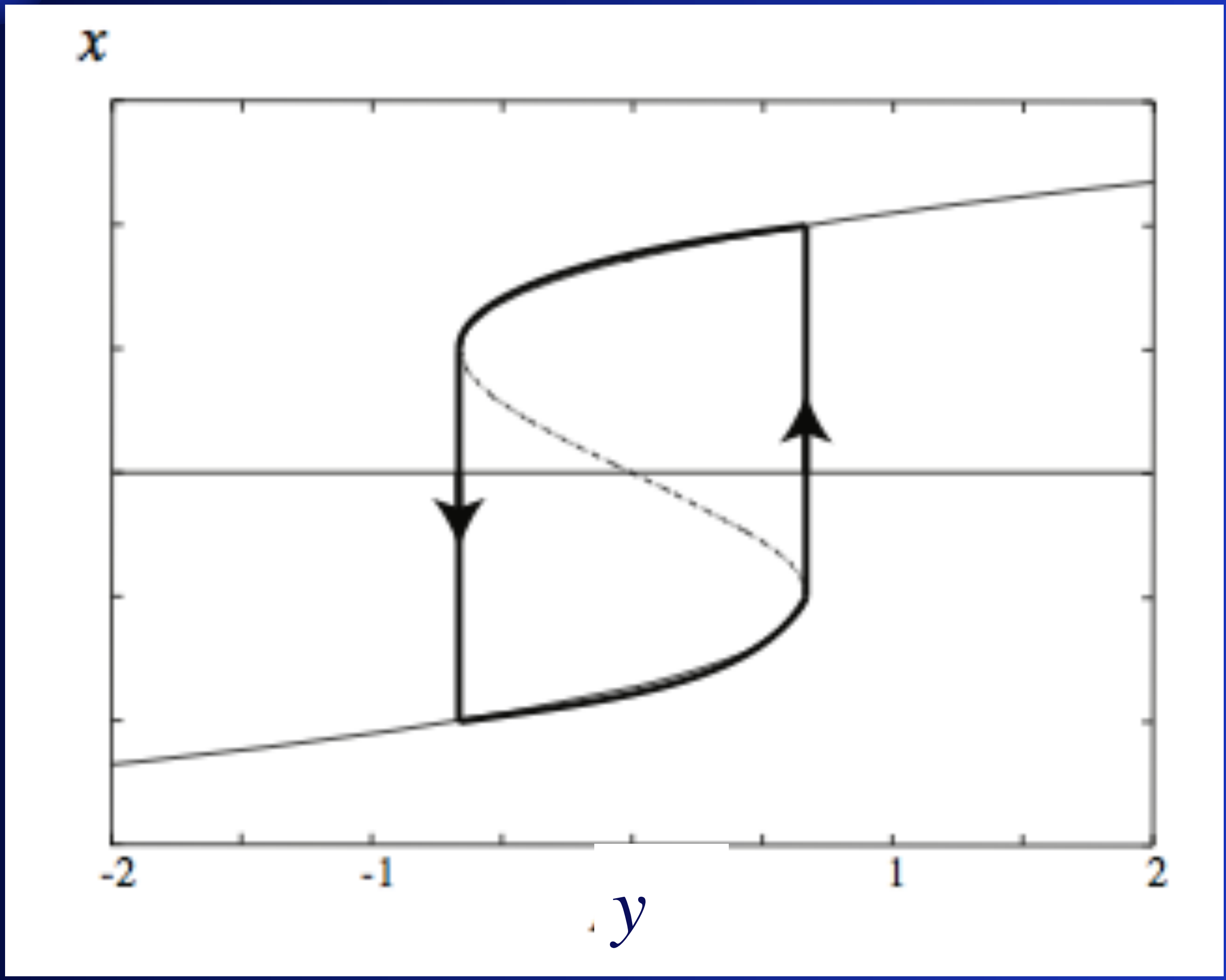


The curve *dx/dt=0*

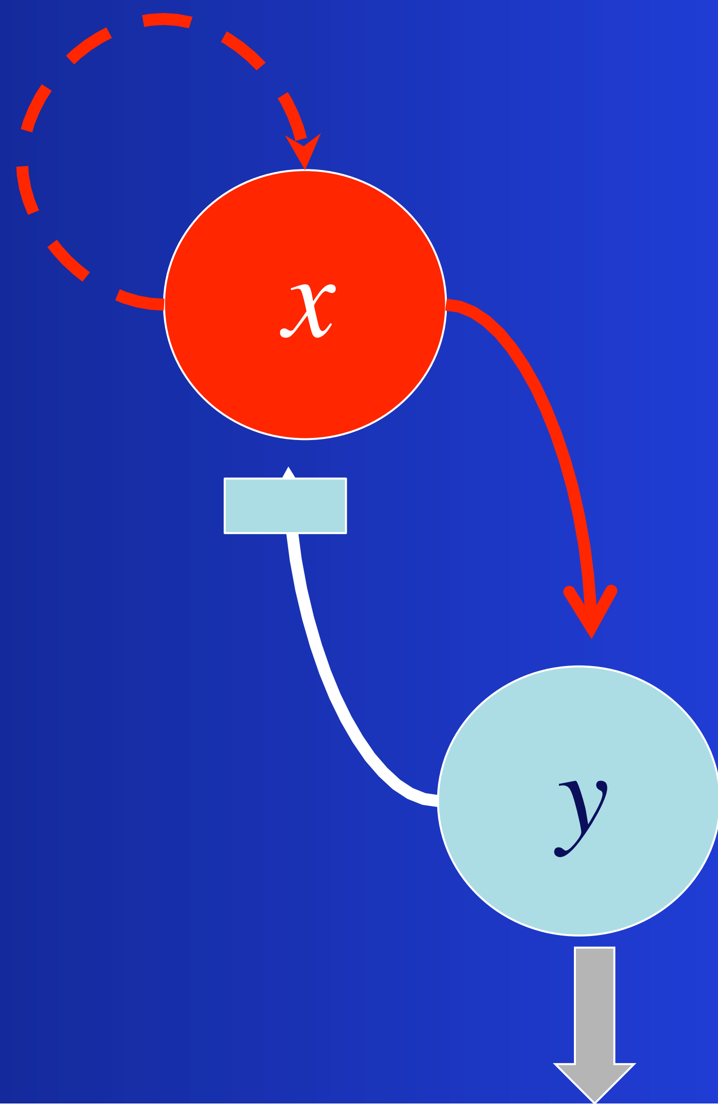
y controls the switch



As y varies, we can go around the hysteresis loop



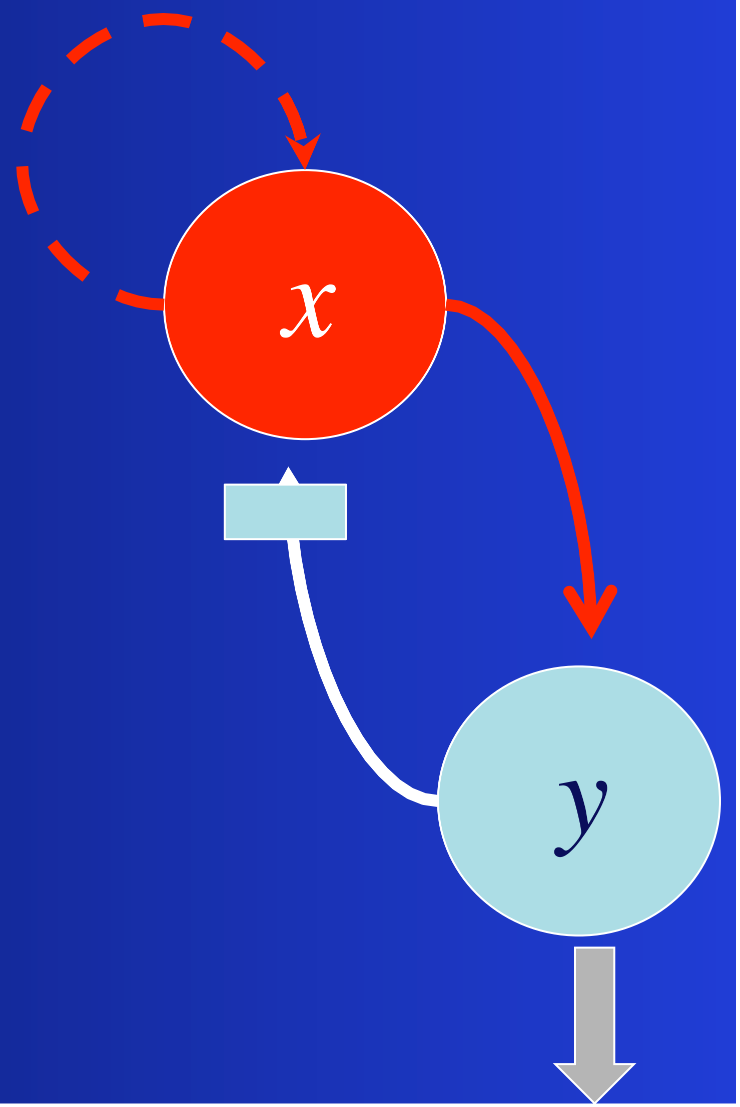
Add negative feedback to the switch



Now y is dynamic

$$\frac{dx}{dt} = c\left[x - \frac{1}{3}x^3 - y \quad \right]$$

$$\frac{dy}{dt} = \frac{1}{c}[x + a - by]\ .$$



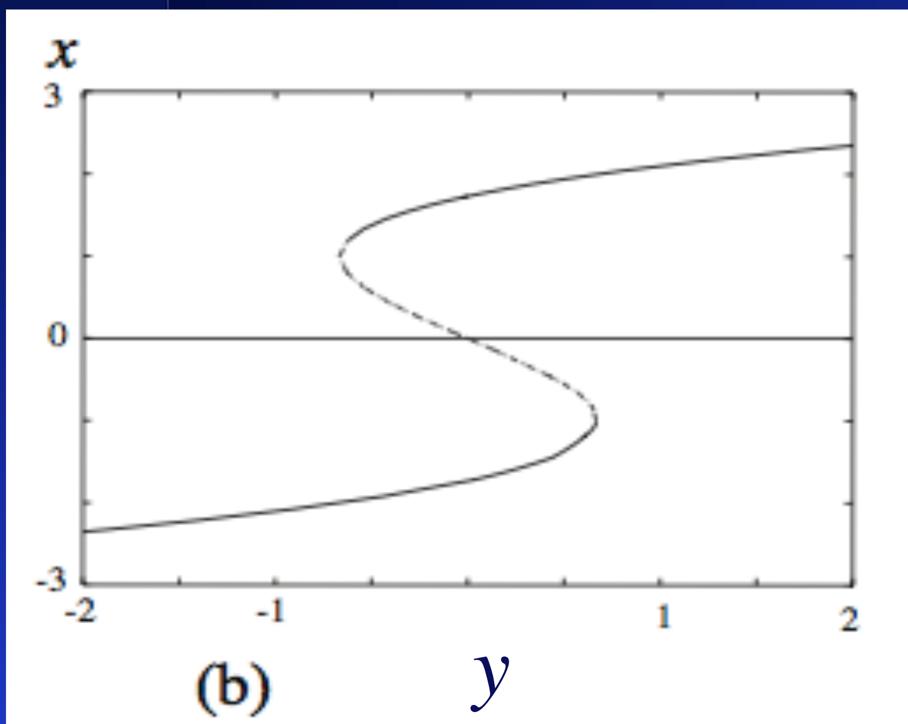
Switch becomes an oscillator

$$\frac{dx}{dt} = c\left[x - \frac{1}{3}x^3 - y\right]$$
$$\frac{dy}{dt} = \frac{1}{c}[x + a - by]\,.$$

Example:
This is the Fitzhugh Nagumo model

“Switch” (Generic bistability)

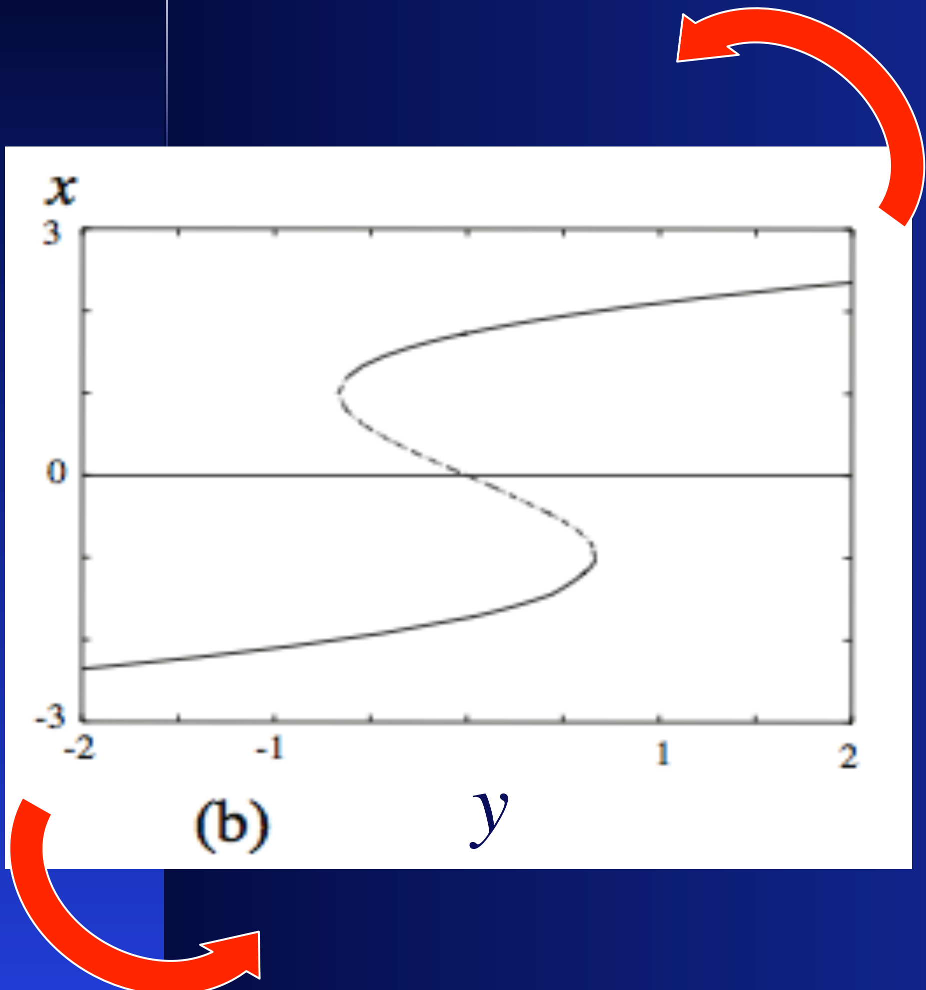
$$\frac{dx}{dt} = c\left(x - \frac{1}{3}x^3 + y\right)$$



Bifurcation diagram

“Switch” (Generic bistability)

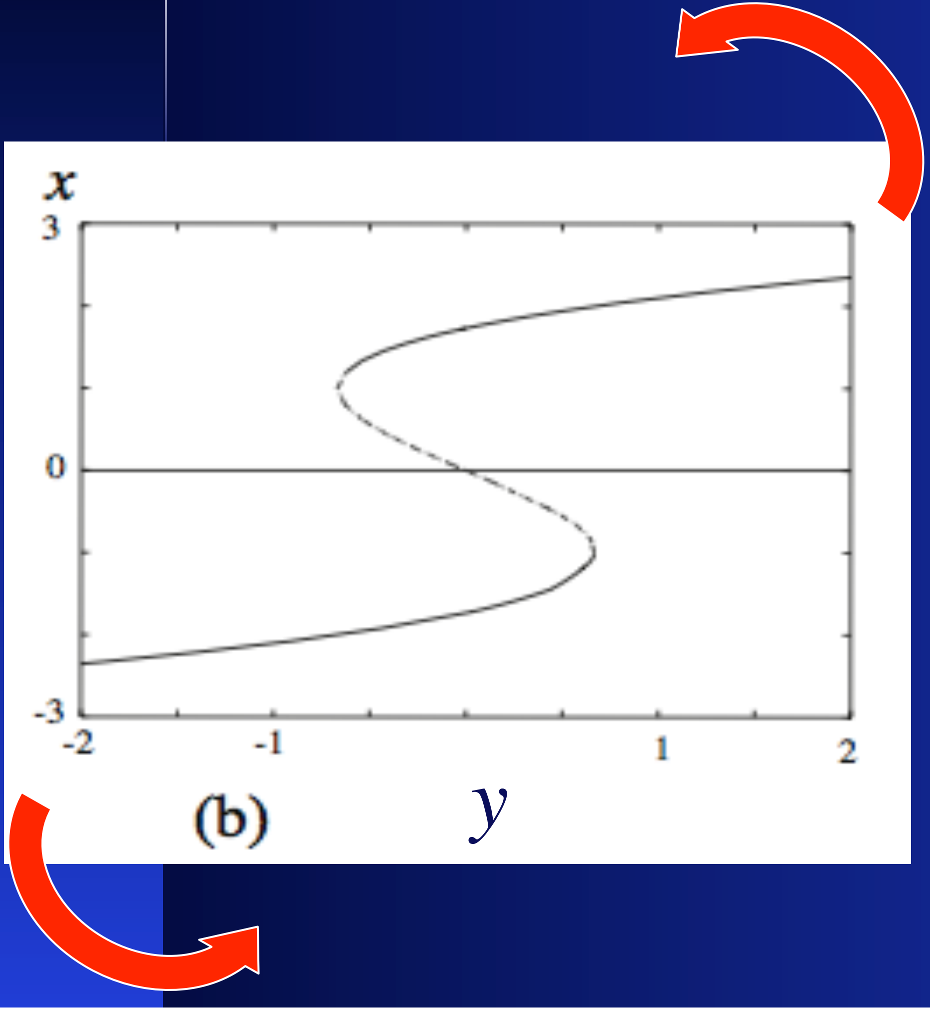
$$\frac{dx}{dt} = c\left(x - \frac{1}{3}x^3 + y\right)$$

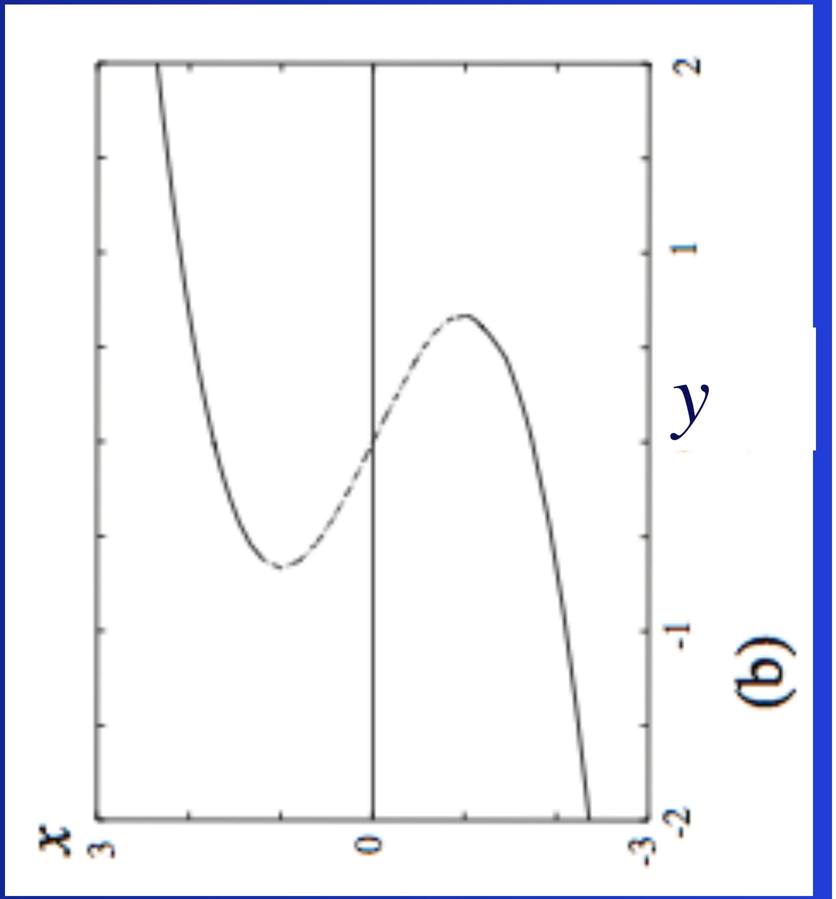


Let us flip it over

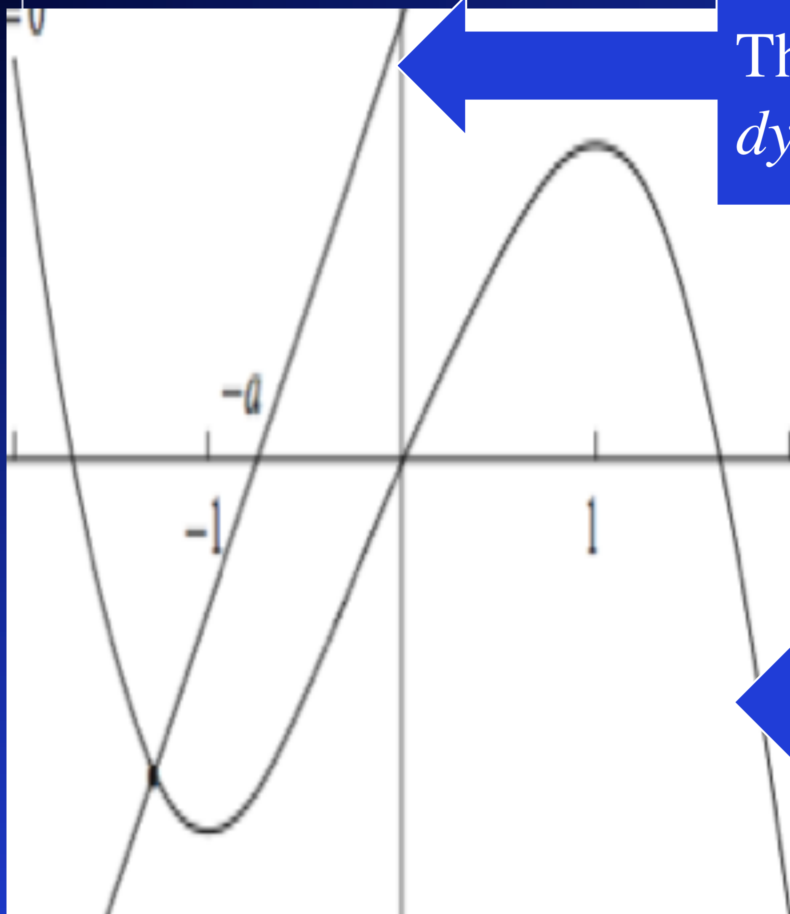
"Switch" (Generic bistability)

$$\frac{dx}{dt} = c\left(x - \frac{1}{3}x^3 + y\right)$$





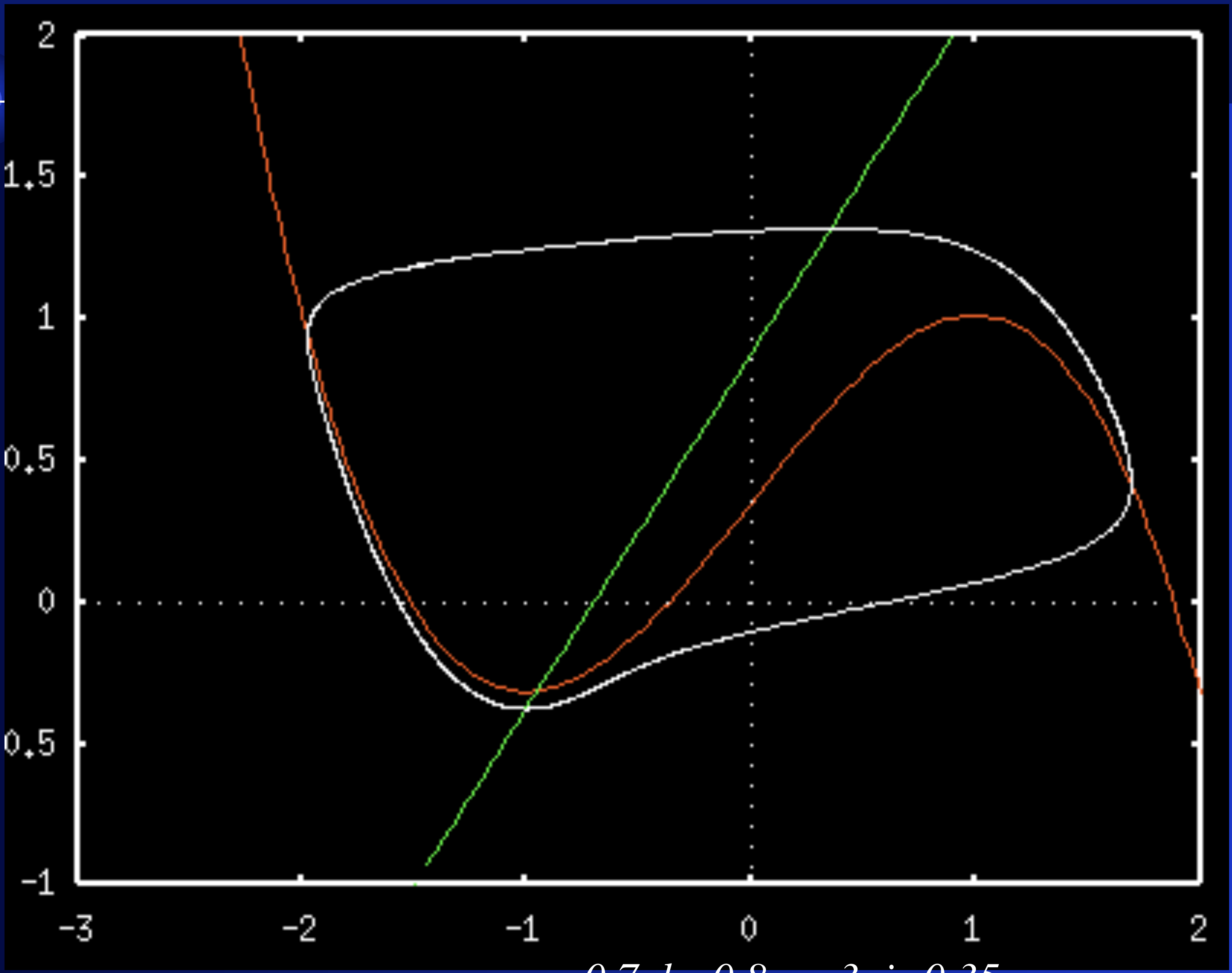
The *xy* phase plane



The curve
dy/dt=0

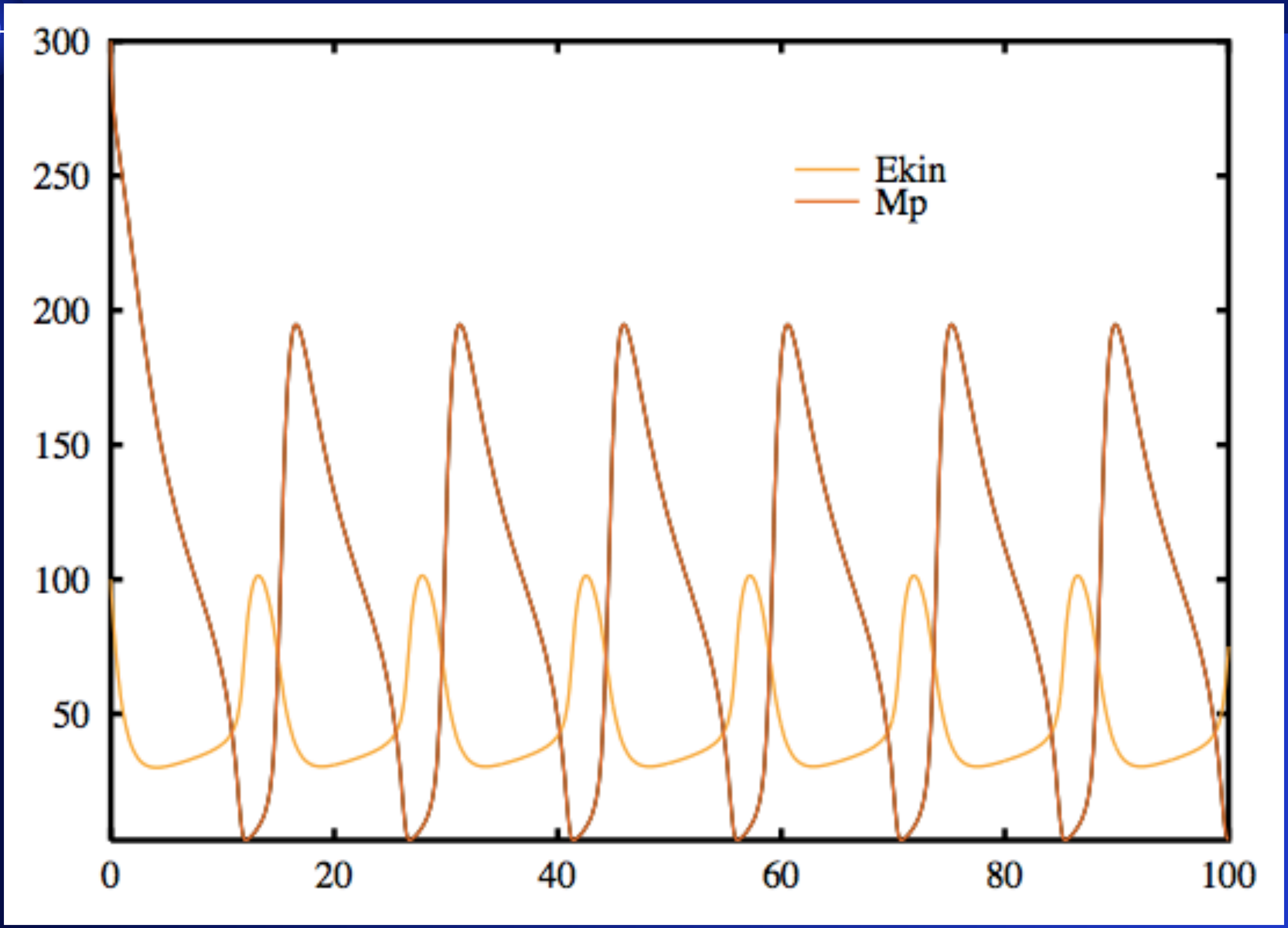
The curve
dx/dt=0

Oscillator



a=0.7, b=0.8, c=3, j=0.35

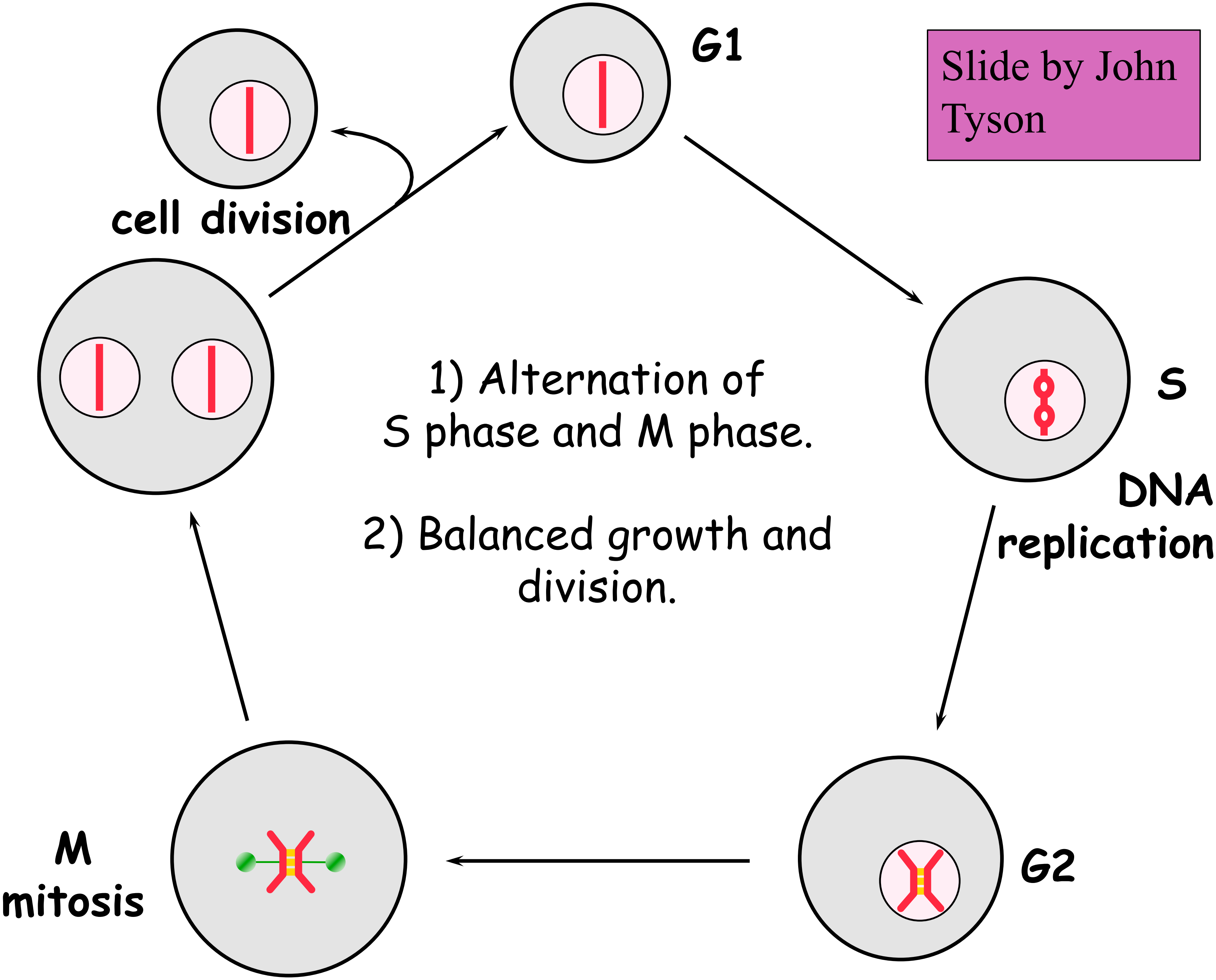
Get an oscillator



Application to the Cell Cycle

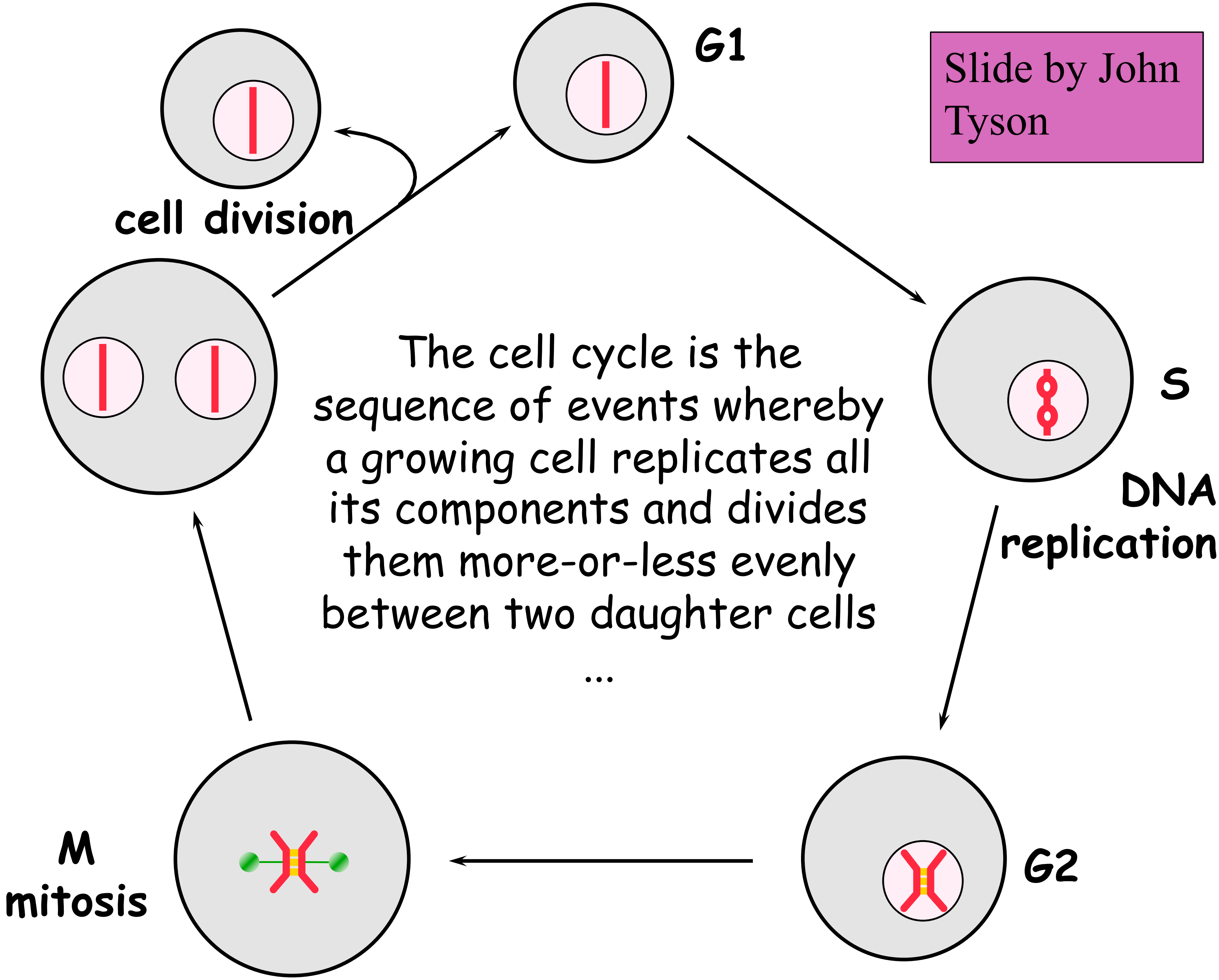
- Work by John Tyson (Virginia Tech):

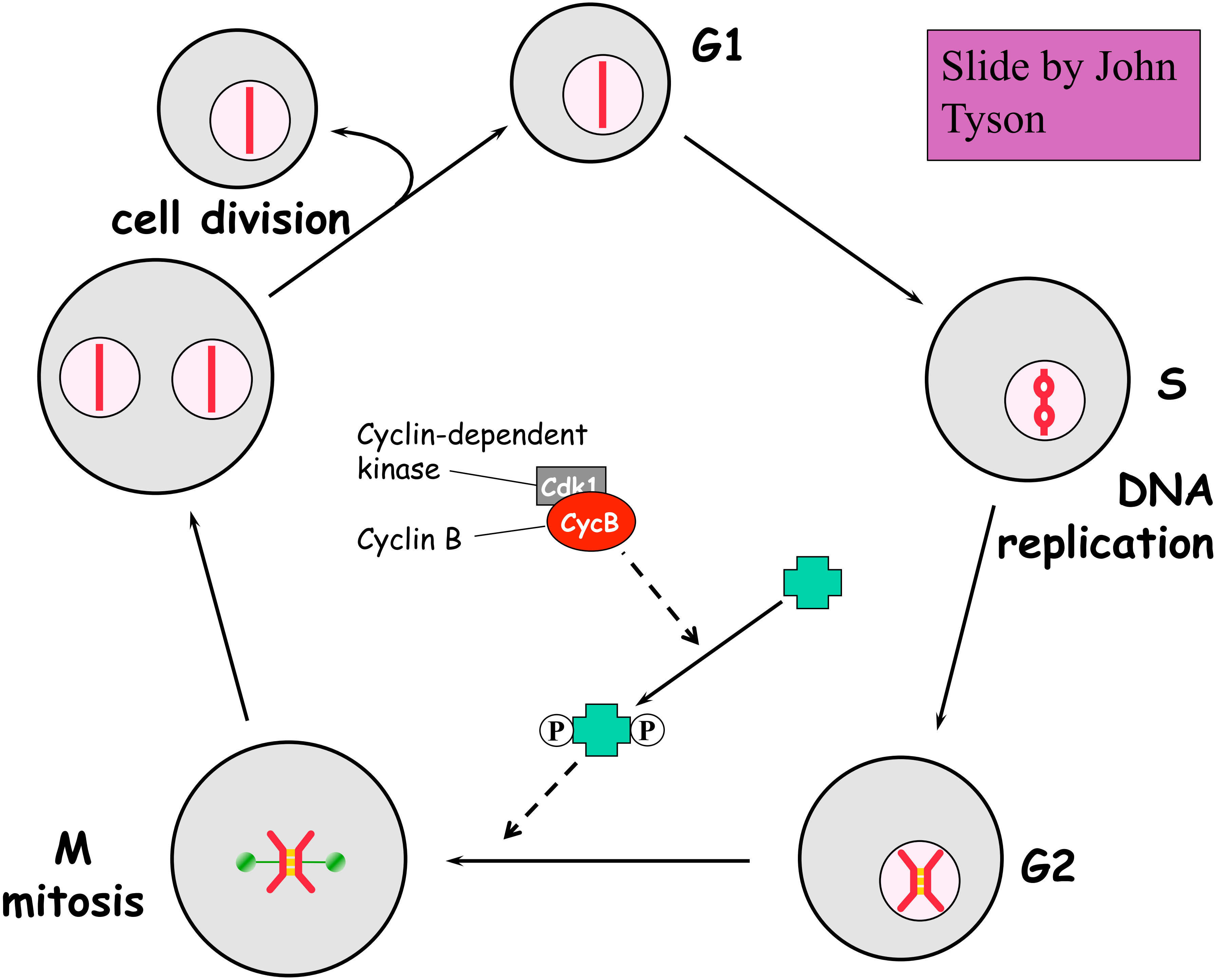
- The control of the cell division is maintained by an intricate web of signaling pathways, that incorporates many signals to decide when to divide.
- The cycle has "checkpoints" at which decisions are made.

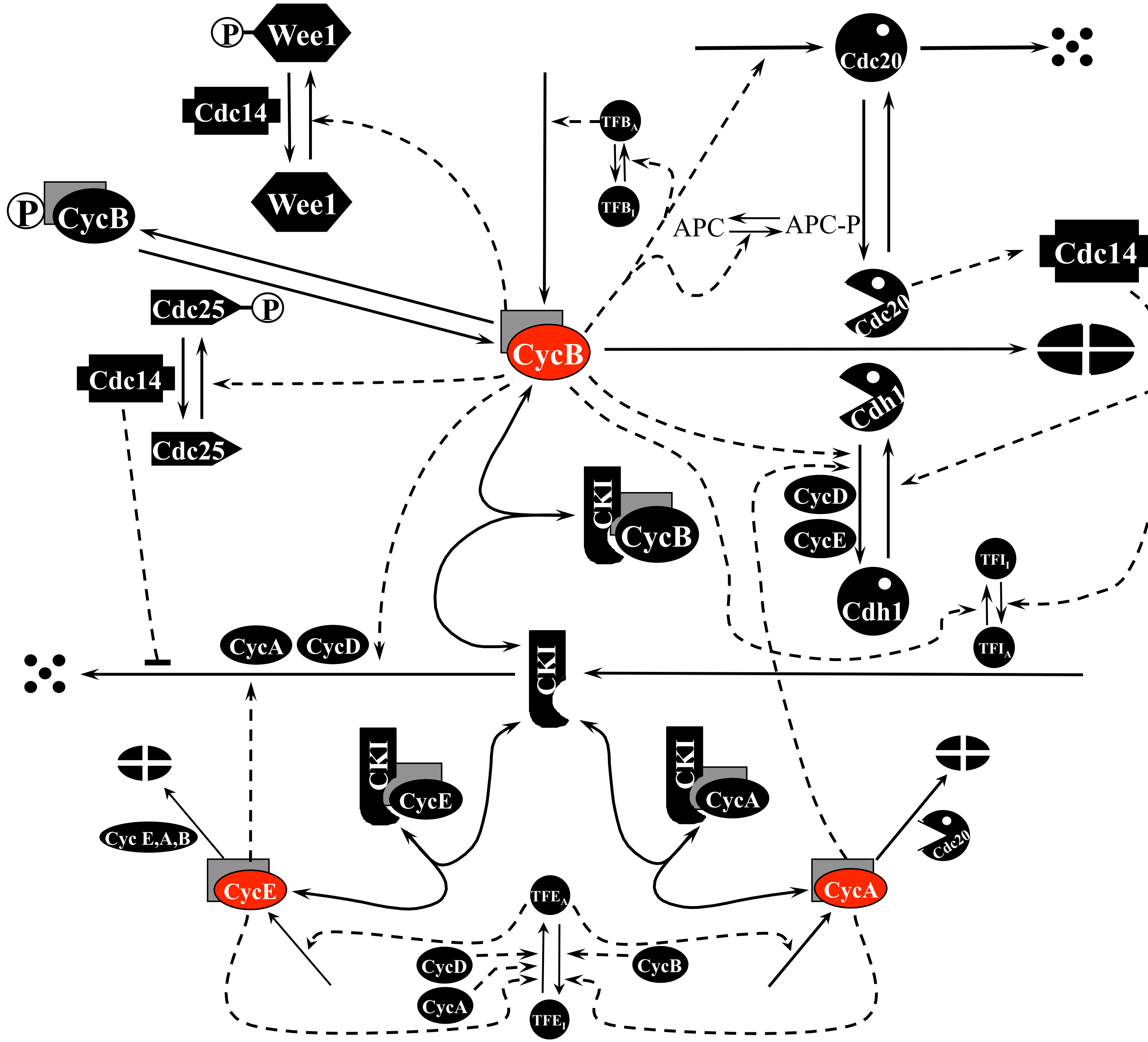


Slide by John Tyson
G1
cell division
S
DNA replication
G2
M
mitosis
1) Alternation of S phase and M phase.
2) Balanced growth and division.

Slide by John Tyson

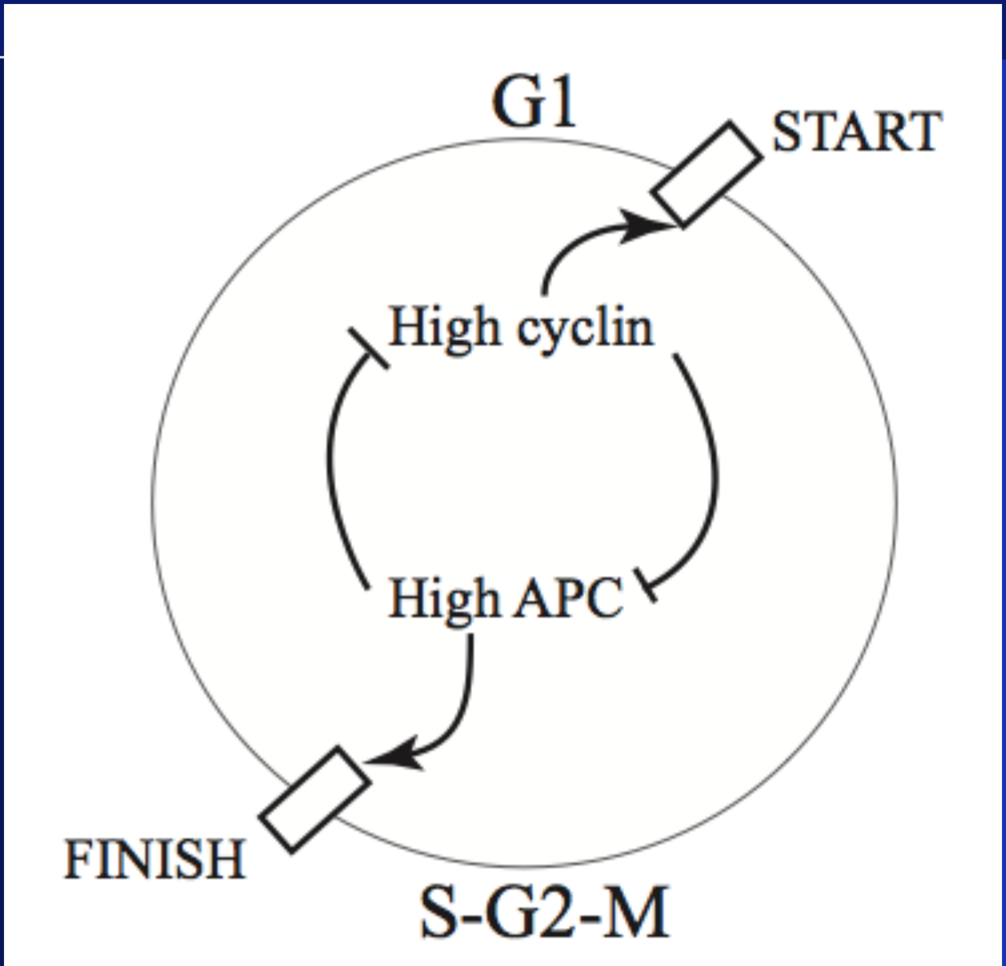



G1
Slide by John Tyson
cell division
S
DNA replication
Cyclin-dependent kinase
Cdk1
CycB
Cyclin B
P
P
M mitosis
G2

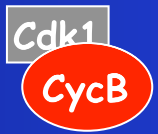

P
Wee1
Cdc14
Wee1
Cdc20
TFB$_A$
TFB$_I$
APC
APC-P
P
CycB
Cdc14
Cdc25
P
Cdc20
Cdc14
CycB
Cdh1
Cdc25
CycD
CycE
CKI
CycB
TFI$_I$
Cdh1
TFI$_A$
CycA
CycD
CKI
CKI
CycE
CKI
CycA
Cdc20
Cyc E,A,B
CycE
TFE$_A$
CycA
CycD
CycB
CycA
TFE$_I$

Checkpoints

in phase G1 there is low Cdk and low cyclin

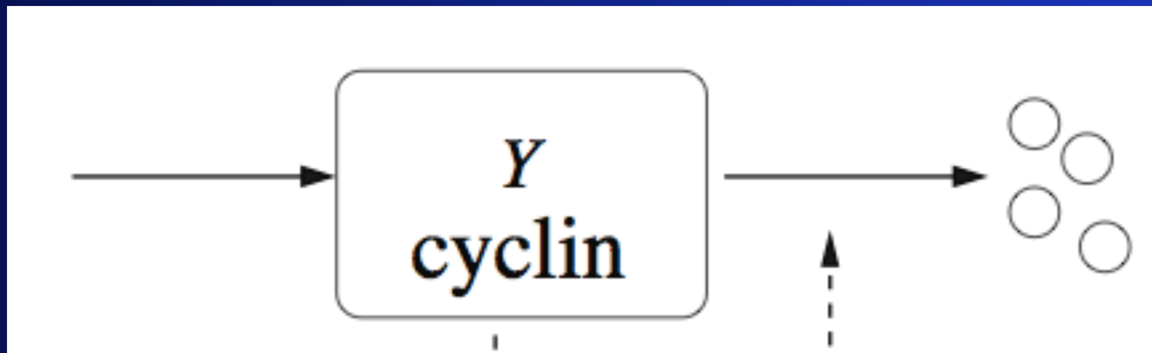


buildup of cyclin/Cdk



APC is activated, leading to destruction of cyclin and loss of CdK activity.

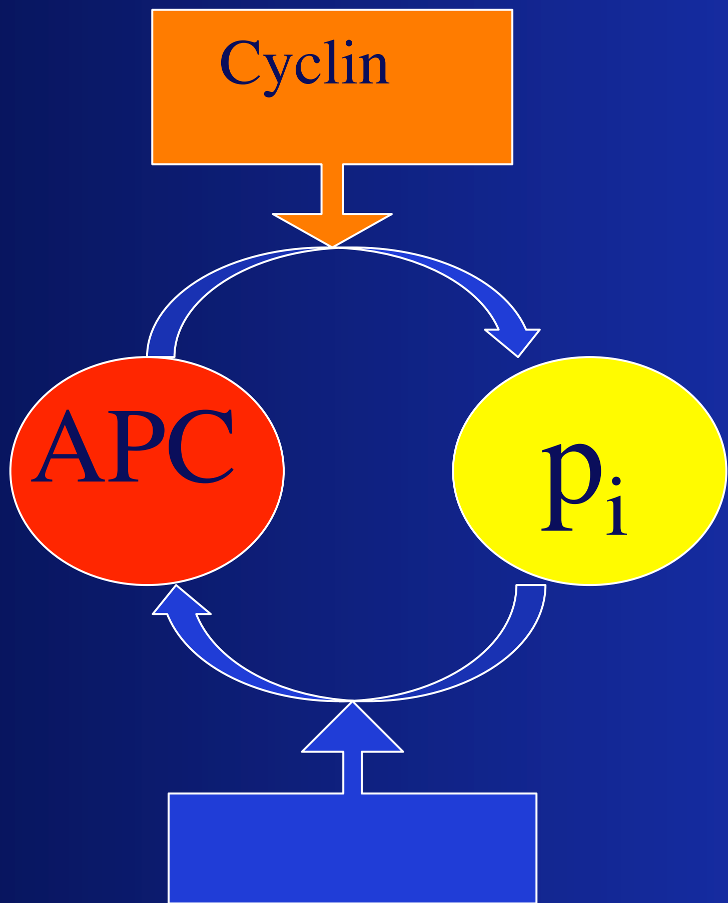
Cyclin is produced and degraded



$$\text{cyclin:} \qquad \frac{dY}{dt} = k_1 - (k_{2p} + k_{2pp}P)Y,$$

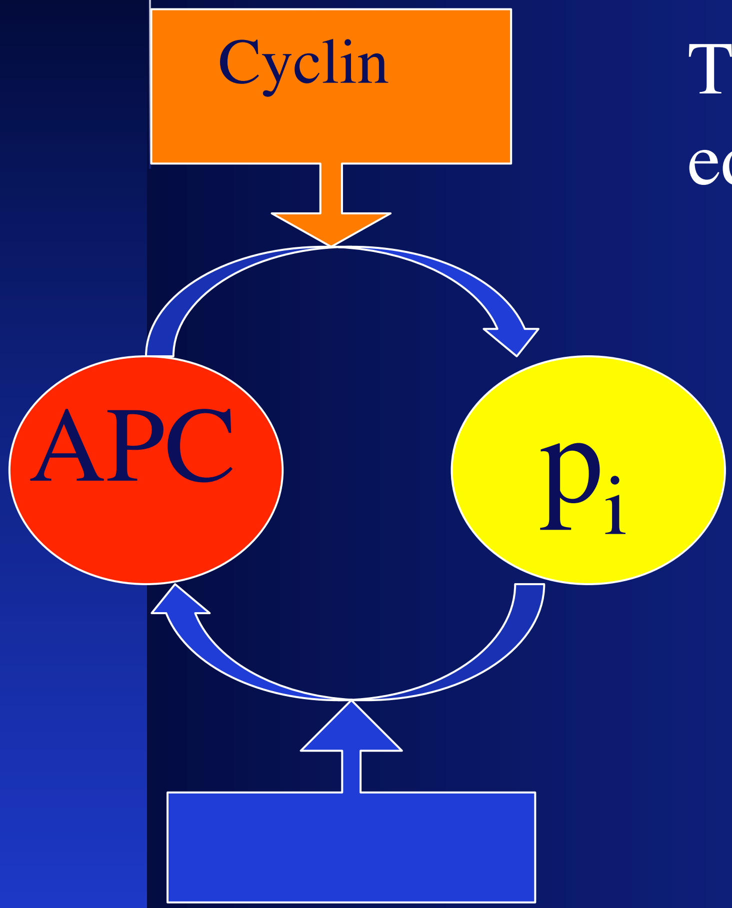
APC is inactivated by phosphorylation

Active form
(no phosphate)



Inactive
form

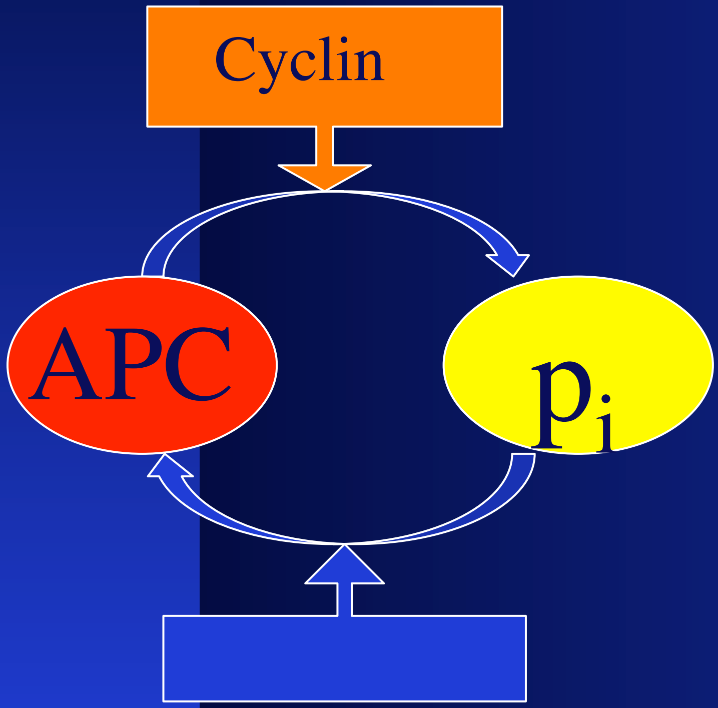
APC is inactivated by phosphorylation

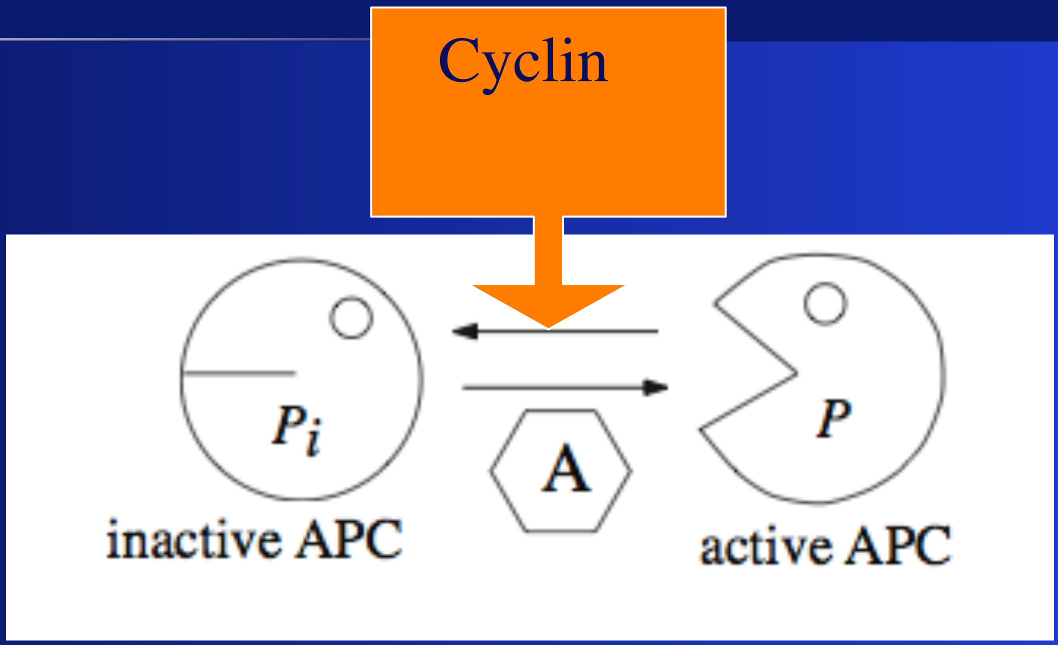


This will be modeled by a typical equation that we have already seen.

$$\frac{dP}{dt} = \frac{V_i P_i}{J_3 + P_i} - \frac{V_a P}{J_4 + P}.$$

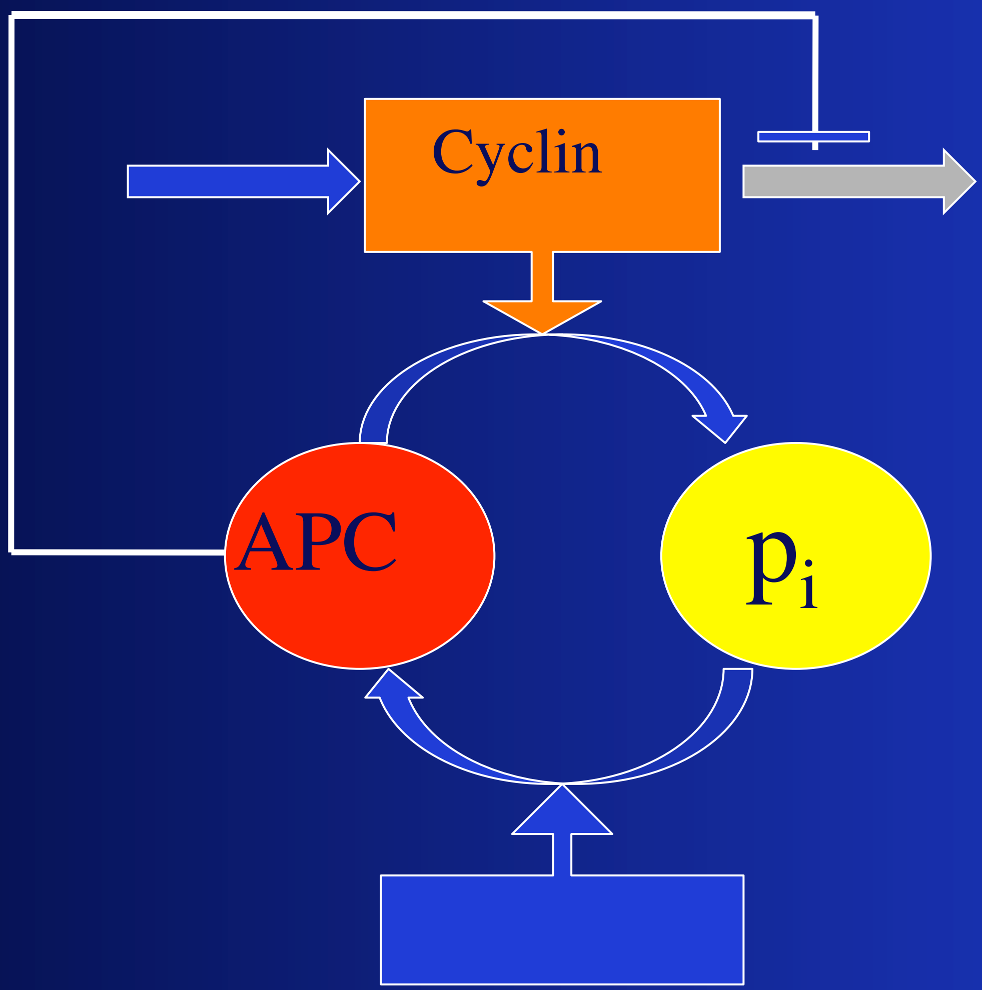
Schematic



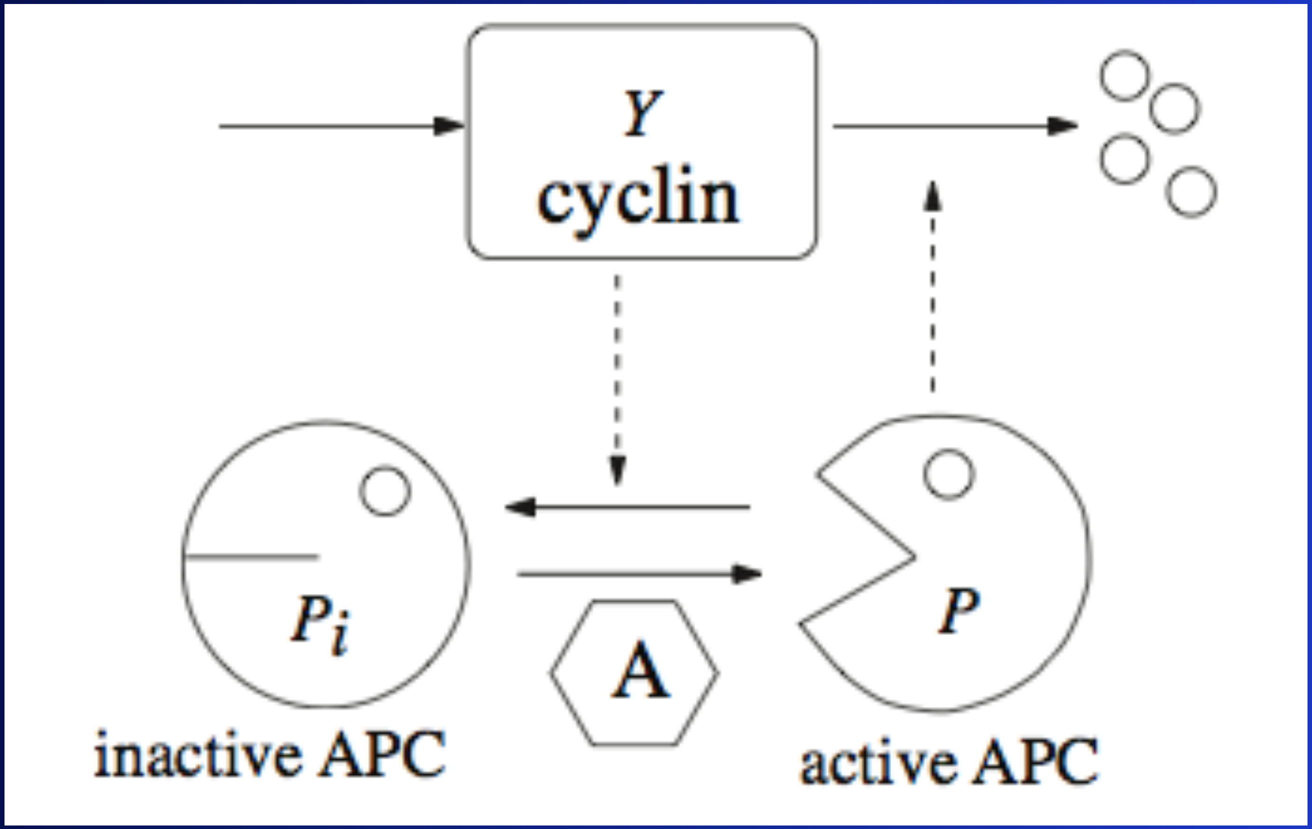


$$\frac{dP}{dt} = \frac{V_i P_i}{J_3 + P_i} - \frac{V_a P}{J_4 + P}.$$

Negative feedback

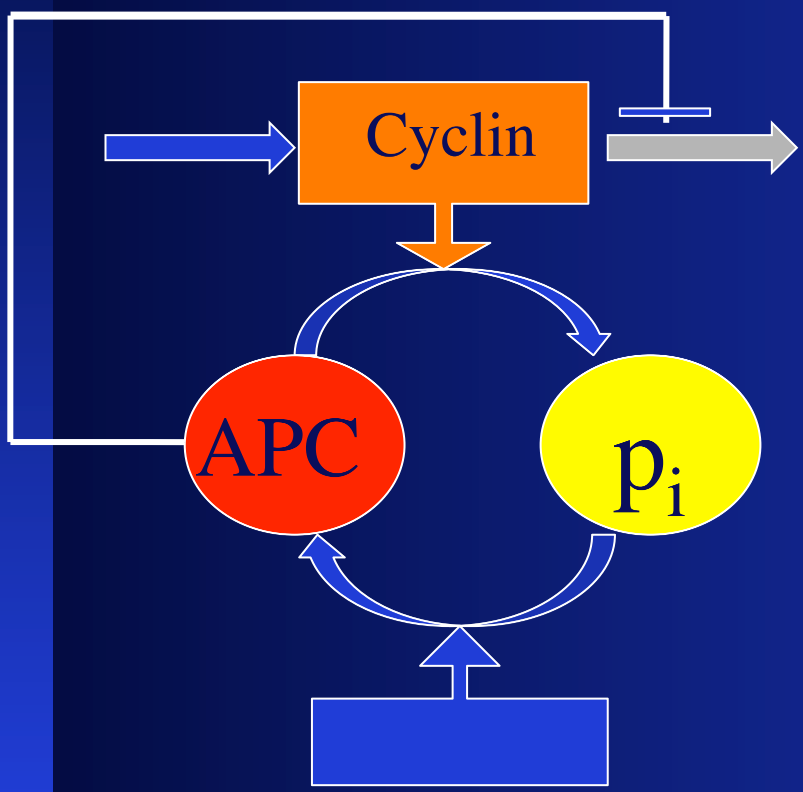


APC and Cyclin mutually antagonistic



$$\text{cyclin:} \quad \frac{dY}{dt} = k_1 - (k_{2p} + k_{2pp}P)Y,$$

$$\text{APC:} \quad \frac{dP}{dt} = \frac{V_i P_i}{J_3 + P_i} - \frac{V_a P}{J_4 + P}.$$



Model

cyclin: $$\frac{dY}{dt} = k_1 - (k_{2p} + k_{2pp}P)Y,$$

APC: $$\frac{dP}{dt} = \frac{V_i P_i}{J_3 + P_i} - \frac{V_a P}{J_4 + P}.$$

Model

$$\frac{dY}{dt} = k_1 - (k_{2p} + k_{2pp}P)Y,$$

$$\frac{dP}{dt} = \frac{(k_{3p} + k_{3pp}A)P_i}{J_3 + P_i} - k_4 m \frac{YP}{J_4 + P}.$$

$$P_i = 1 - P.$$

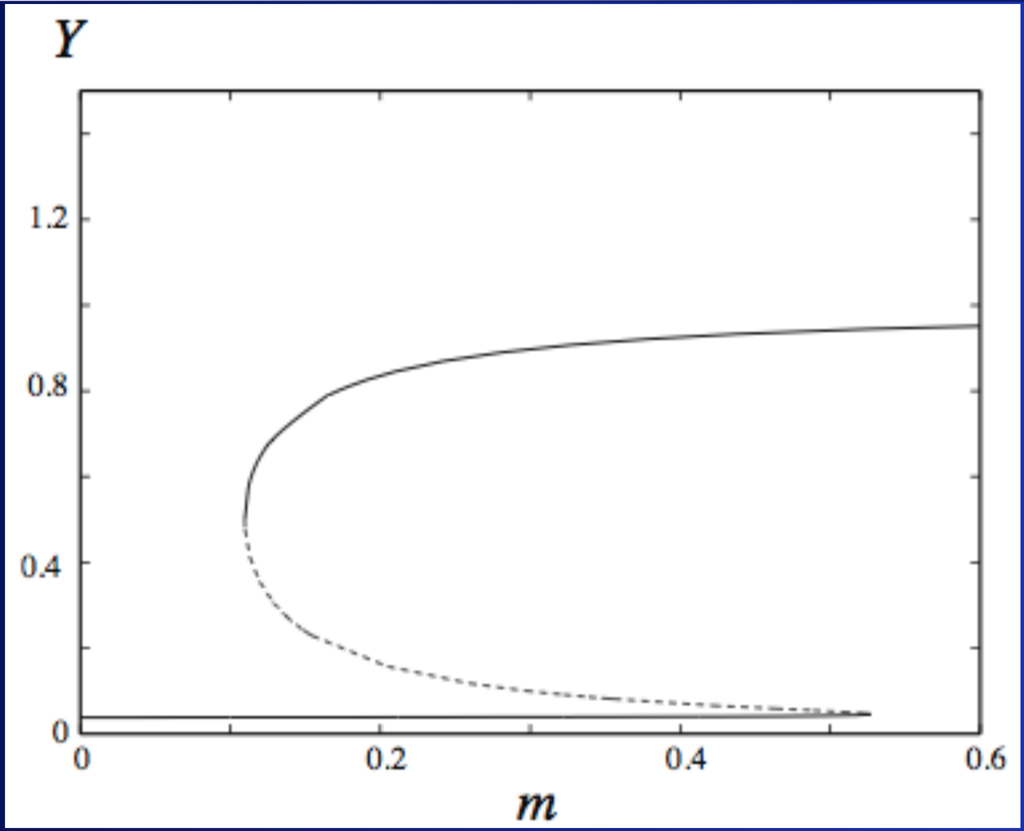
Model

$$\frac{dY}{dt} = k_1 - (k_{2p} + k_{2pp}P)Y,$$

$$\frac{dP}{dt} = \frac{(k_{3p} + k_{3pp}A)(1-P)}{J_3 + (1-P)} - k_4 m \frac{YP}{J_4 + P}.$$

Bistable switch

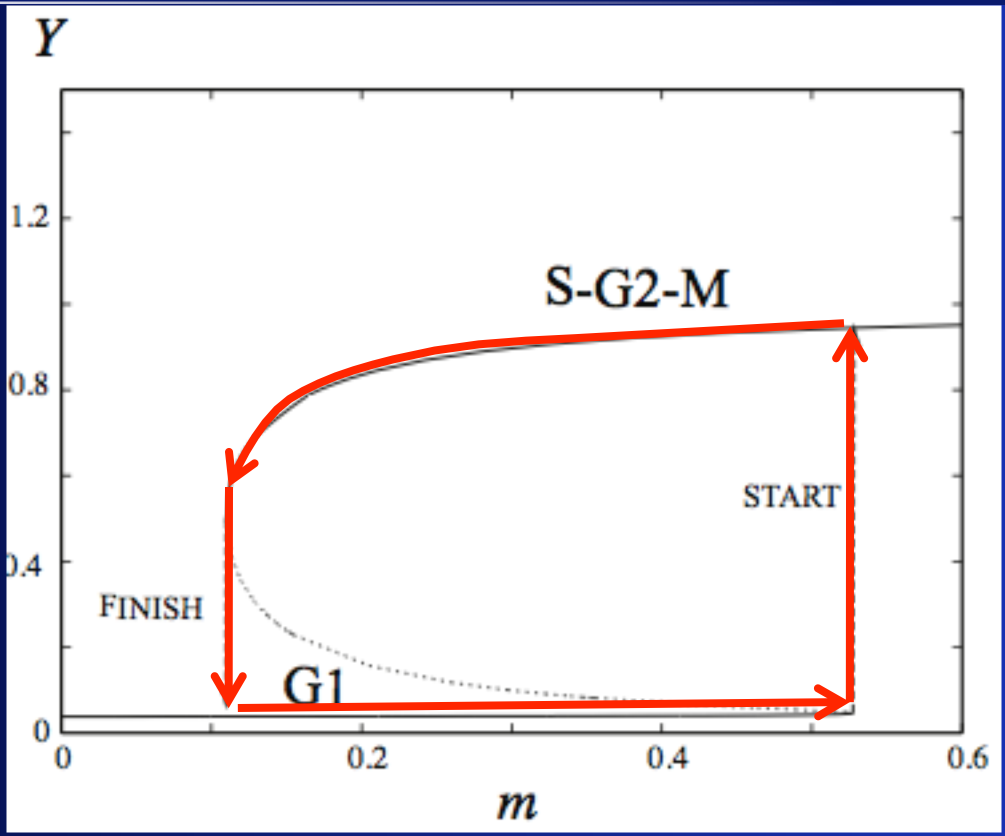
Cyclin



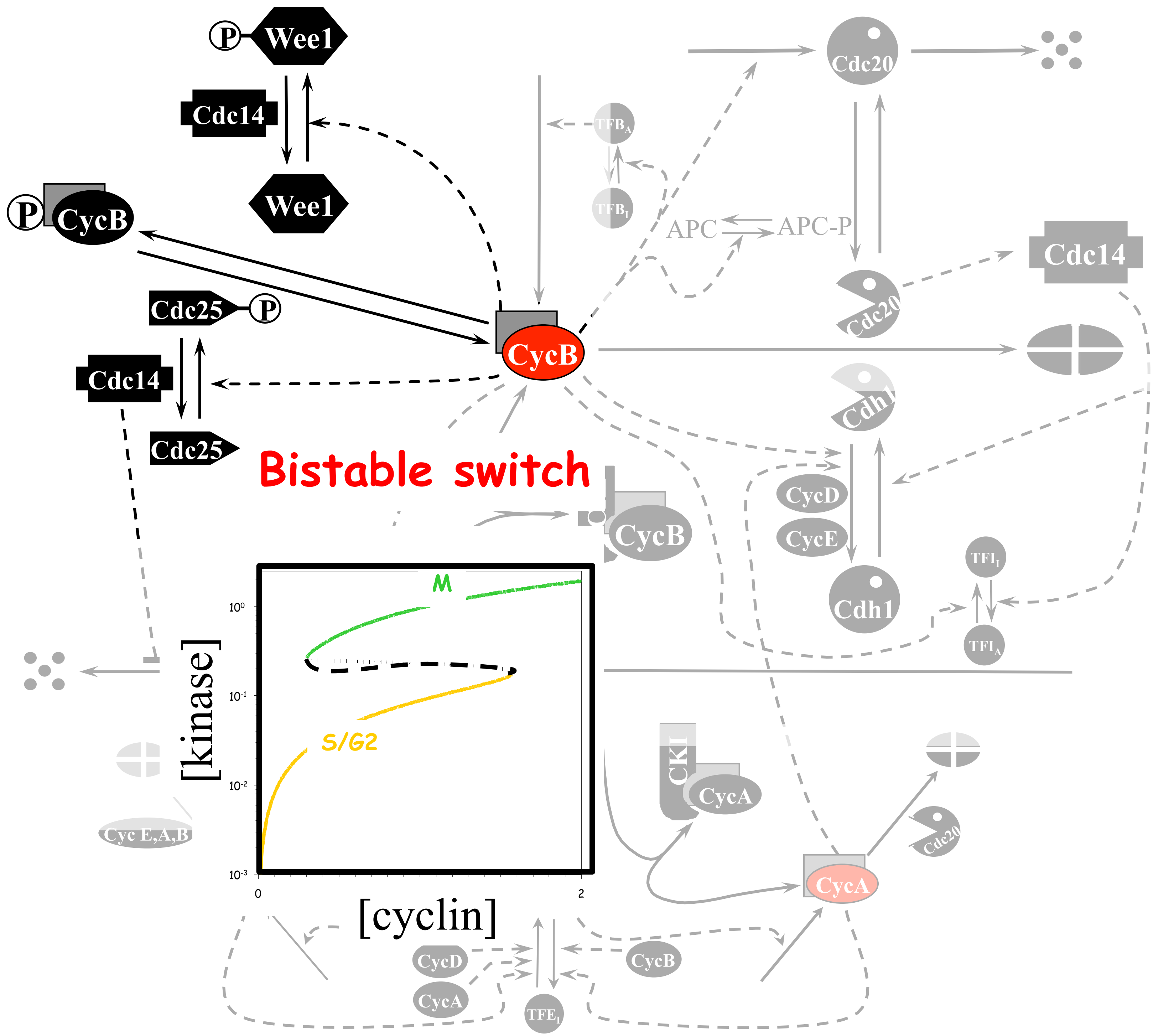
Cell Mass

Cell mass is the parameter that flips the switch

Cyclin

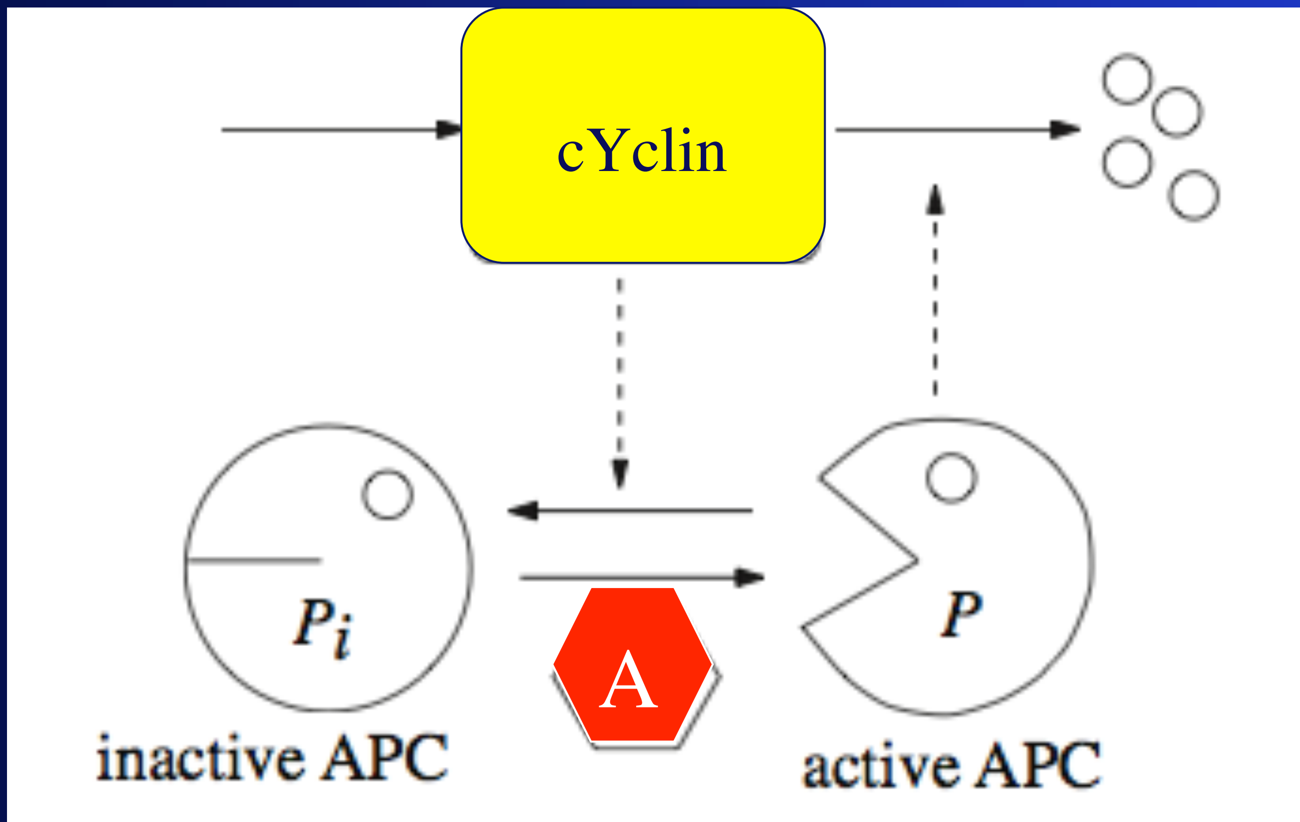


Cell Mass



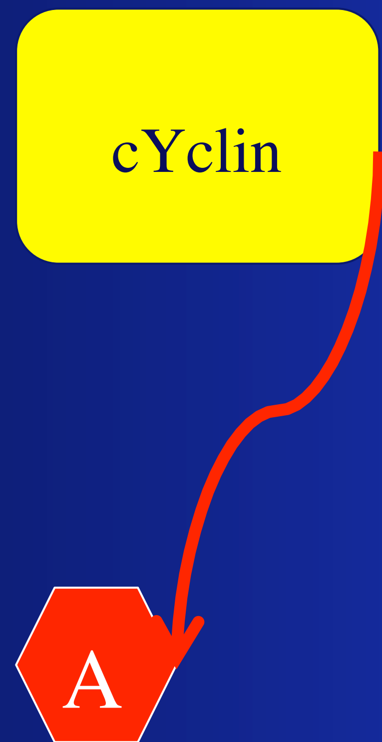
Wee1
Cdc14
Wee1
CycB
Cdc25
Cdc14
Cdc25
CycB
Bistable switch
Cdc20
APC
APC-P
Cdc20
Cdc14
Cdh1
CycD
CycE
Cdh1
CycB
M
S/G2
[kinase]
[cyclin]
CKI
CycA
CycA
Cdc20
Cyc E,A,B
CycD
CycA
CycB

Activation of APC by Cdc20 (“A”)



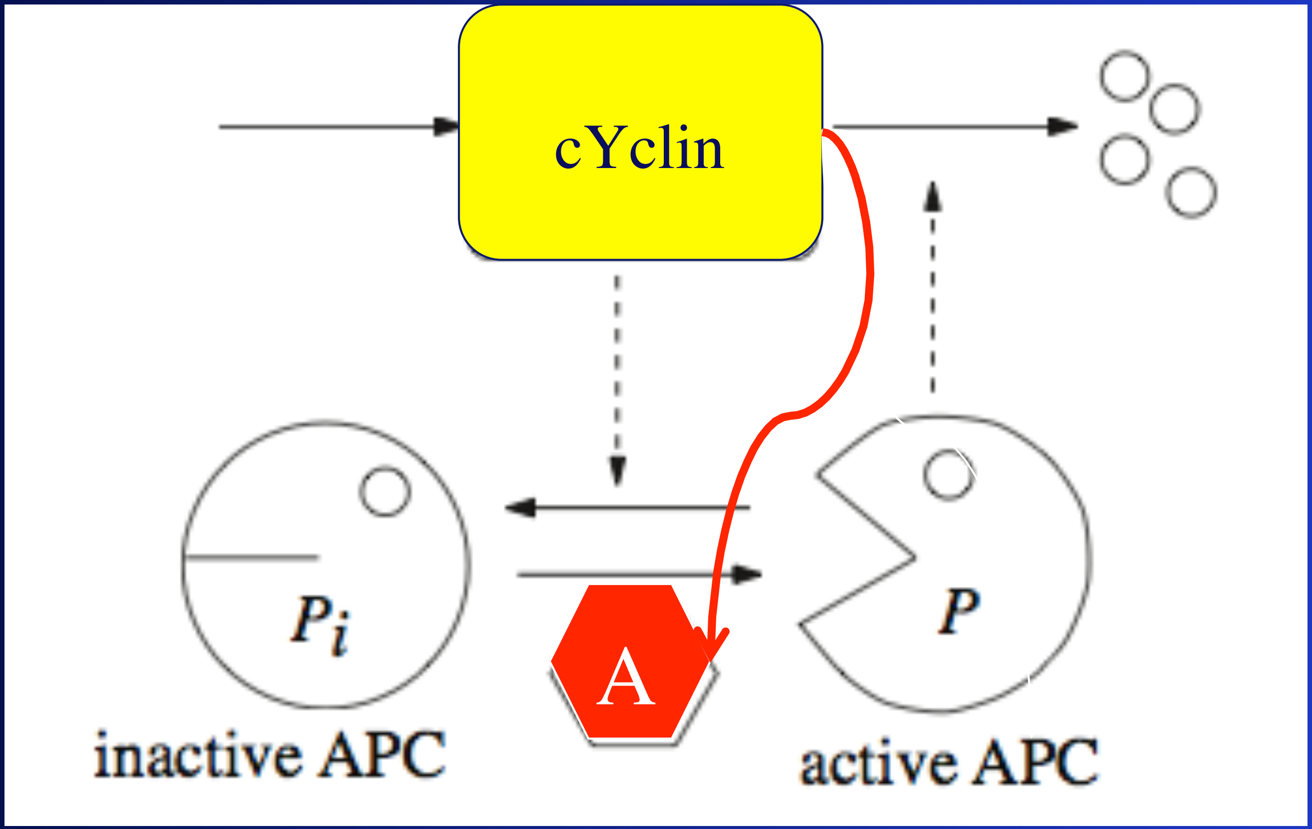
A= Cdc20. It increases sharply during metaphase and activates APC

A is turned on by cyclin (sigmoidally)



$$\frac{dA}{dt} = k_{5p} + k_{5pp} \frac{(mY/J_5)^n}{1+(Ym/J_5)^n} - k_6 A.$$

Activation of APC by Cdc20 (“A”)



A= Cdc20. It increases sharply during metaphase and activates APC

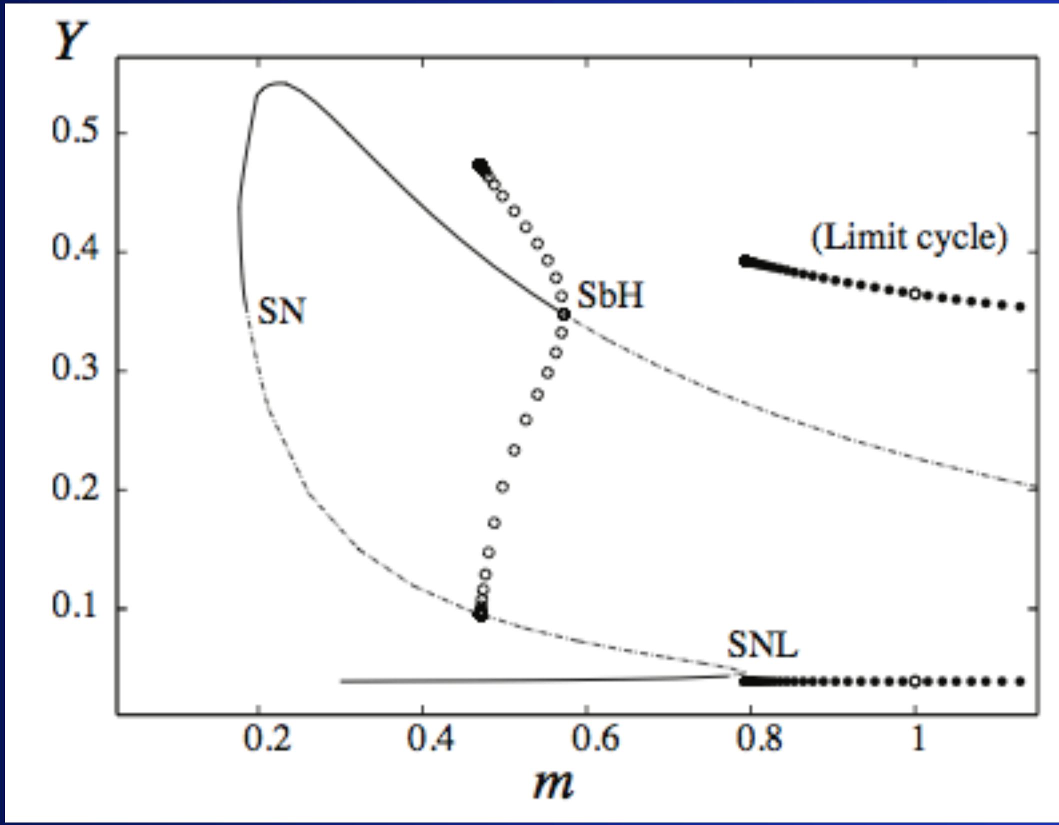
Three variable model:

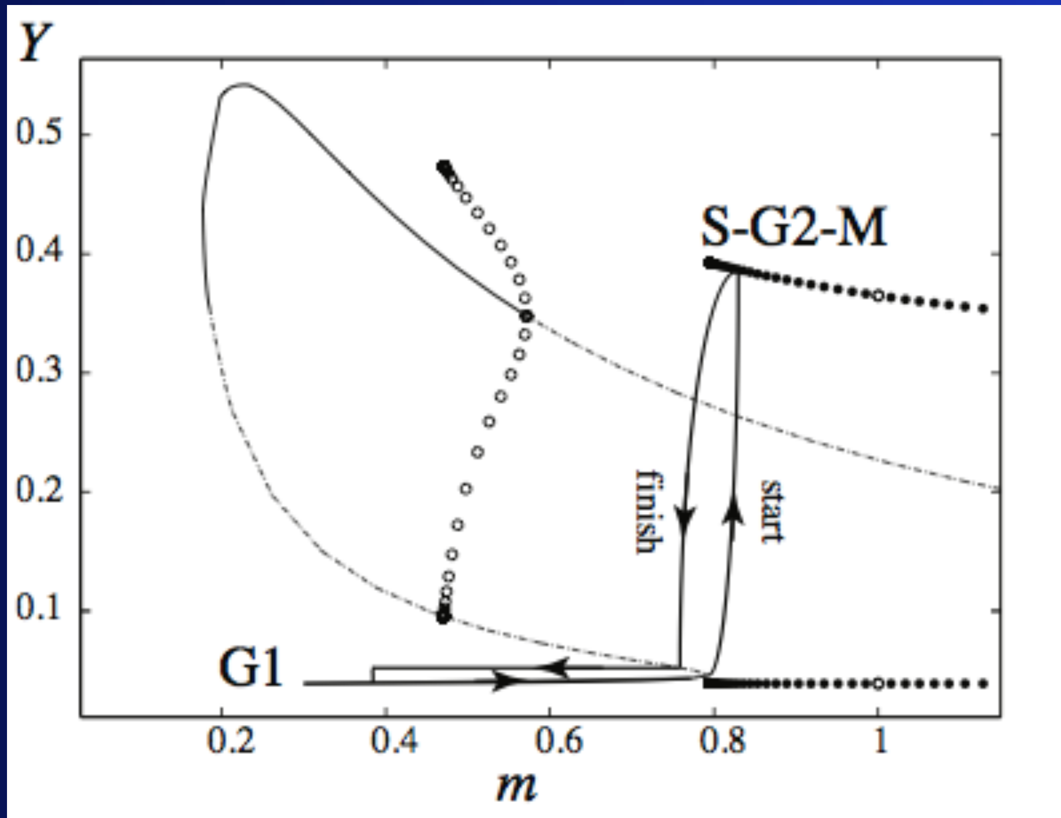
$$\frac{dY}{dt} = k_1 - (k_{2p} + k_{2pp}P)Y,$$

$$\frac{dP}{dt} = \frac{(k_{3p} + k_{3pp}A)(1-P)}{J_3 + (1-P)} - k_4 m \frac{YP}{J_4 + P},$$

$$\frac{dA}{dt} = k_{5p} + k_{5pp}\frac{(mY/J_5)^n}{1 + (Ym/J_5)^n} - k_6 A.$$

Now we get a cell cycle.





Y
0.5
0.4
0.3
0.2
0.1
S-G2-M
finish
start
G1
0.2
0.4
0.6
0.8
1
m