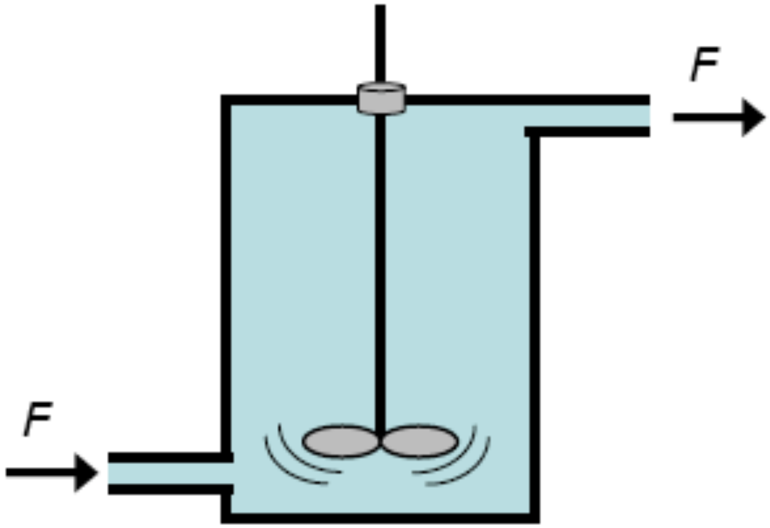
Case Study: Cell Cycle Control Mechanism

Chemostat



F = flow rate (L/s)

V = volume (L)

$M(T)$ = microbe density (#/L)

$N(T)$ = nutrient concen (mol/L)

T = time (s)

$$\frac{dM}{dT} = \frac{N}{K+N} \cdot rM - \frac{F}{V} M, \quad \frac{dN}{dT} = -\alpha \frac{N}{K+N} \cdot rM + \frac{F}{V}\left(N_o - N\right)$$

r = max repro rate,

K = nutrient concen at half-max repro rate

α = conversion factor,

N_o = nutrient concen in feed

Chemostat

$$\frac{dM}{dT} = \frac{N}{K+N} \cdot rM - \frac{F}{V} M, \quad \frac{dN}{dT} = -\alpha \frac{N}{K+N} \cdot rM + \frac{F}{V}\left(N_o - N\right)$$

$$\text{Let } x(t) = \frac{\alpha M(T)}{K}, \; y(t) = \frac{N(T)}{K}, \; t = rT$$

$$\frac{dx}{dt} = \frac{xy}{1+y} - \phi x, \quad \frac{dy}{dt} = -\frac{xy}{1+y} + \phi\left(y_o - y\right)$$

$$\text{where } \phi = \frac{F}{rV}, \; y_o = \frac{N_o}{K} \quad \text{(dimensionless)}$$

Chemostat

$$\frac{dx}{dt} = \frac{xy}{1+y} - \phi x, \quad \frac{dy}{dt} = -\frac{xy}{1+y} + \phi\left(y_o - y\right)$$

Nullclines: $\dot{x} = 0: \quad x = 0 \text{ or } y = \dfrac{\phi}{1-\phi}$

$$\dot{y} = 0: \quad x = \phi \frac{\left(y_o - y\right)\left(1+y\right)}{y}$$

Chemostat

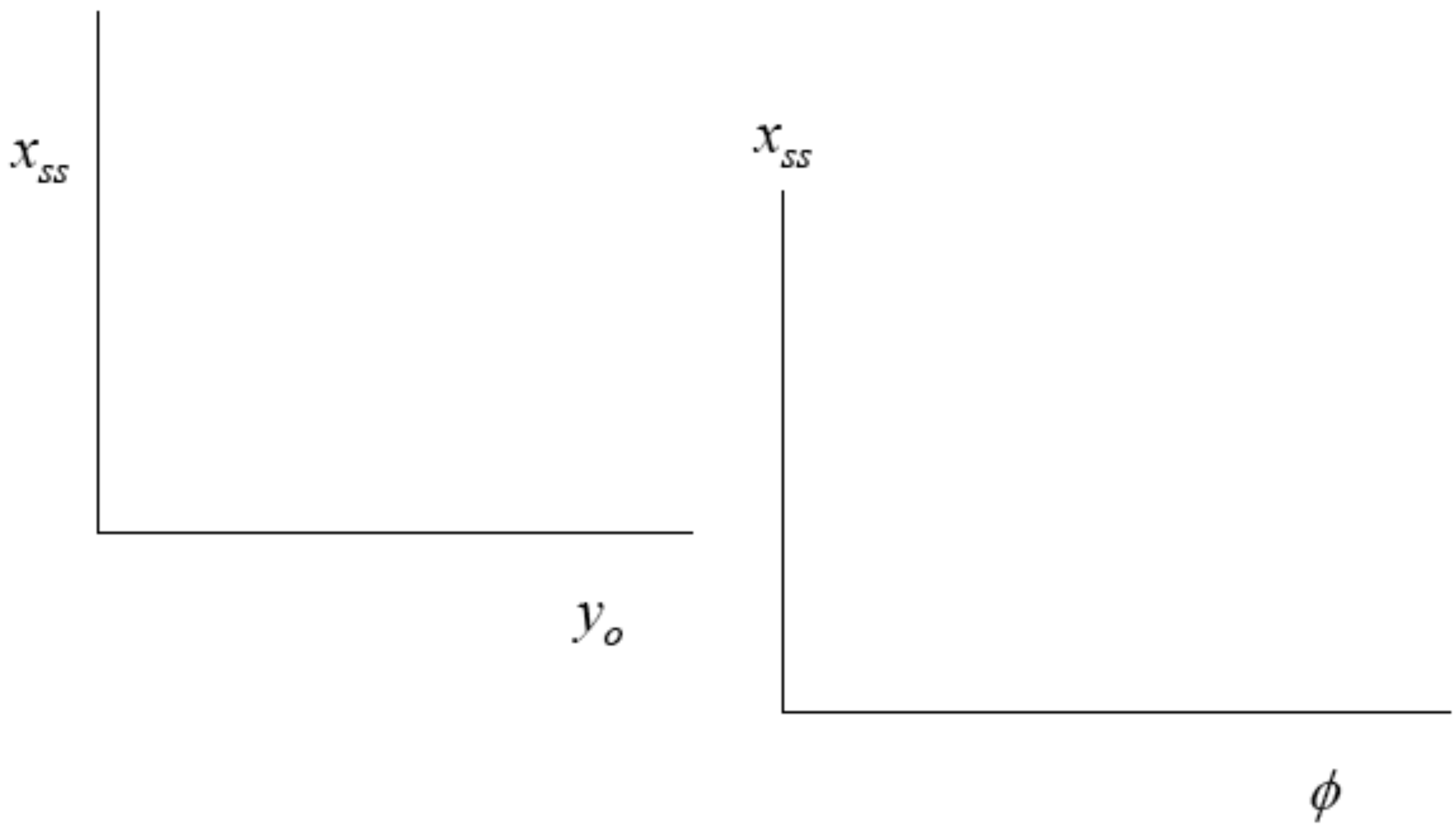
$$\frac{dx}{dt} = \frac{xy}{1+y} - \phi x, \quad \frac{dy}{dt} = -\frac{xy}{1+y} + \phi(y_o - y)$$

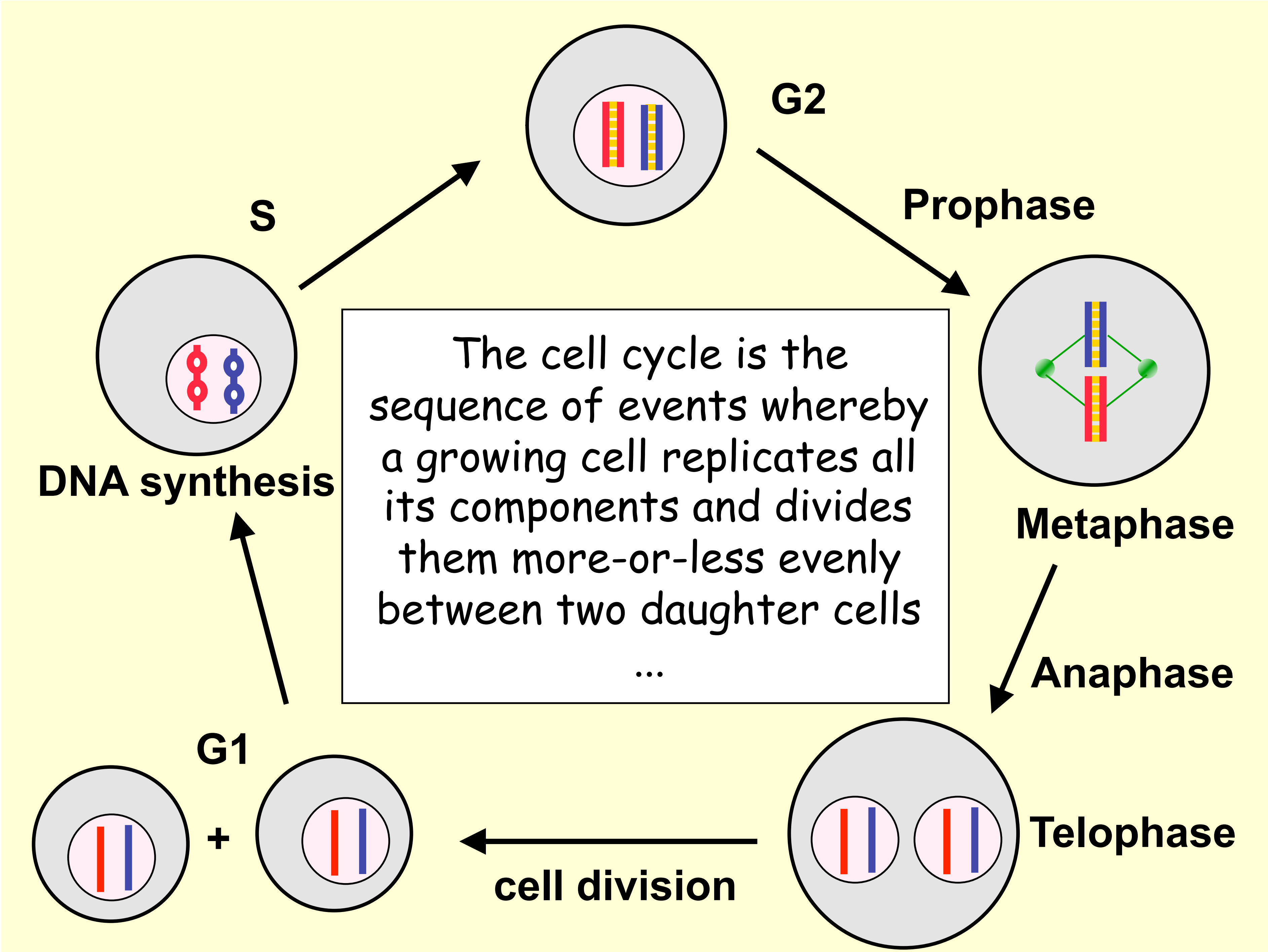
Steady states: (i) $x = 0,\ y = y_o$

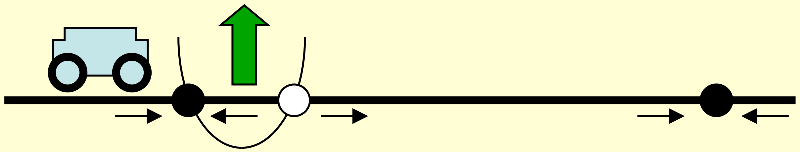
(ii) $x = y_o - \dfrac{\phi}{1-\phi},\ y = \dfrac{\phi}{1-\phi}$

Chemostat

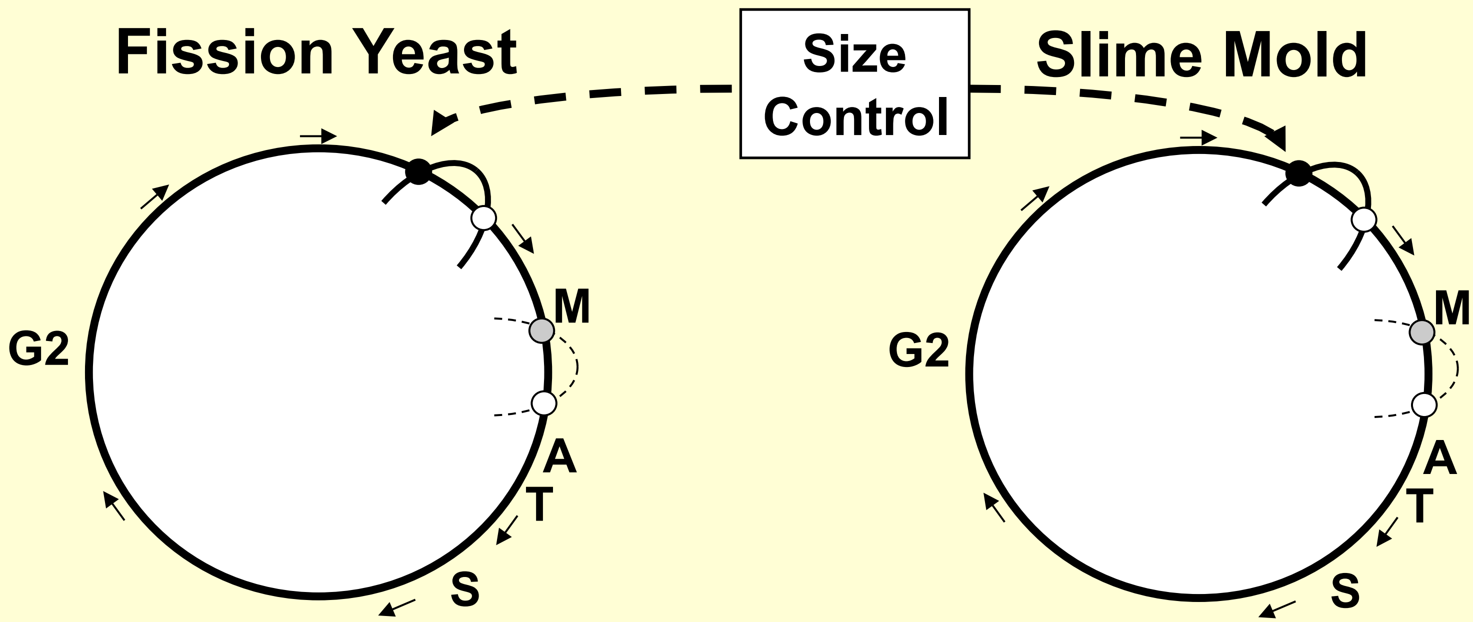
One-parameter Bifurcation Diagrams

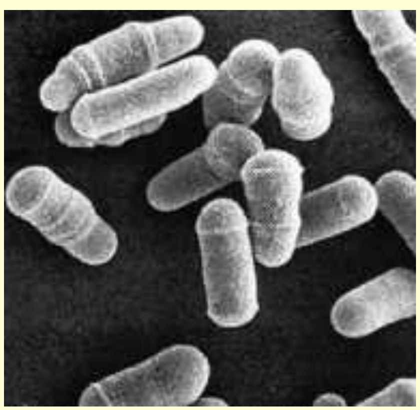



G2
S
Prophase
DNA synthesis
Metaphase
The cell cycle is the sequence of events whereby a growing cell replicates all its components and divides them more-or-less evenly between two daughter cells
...
Anaphase
G1
+
Telophase
cell division

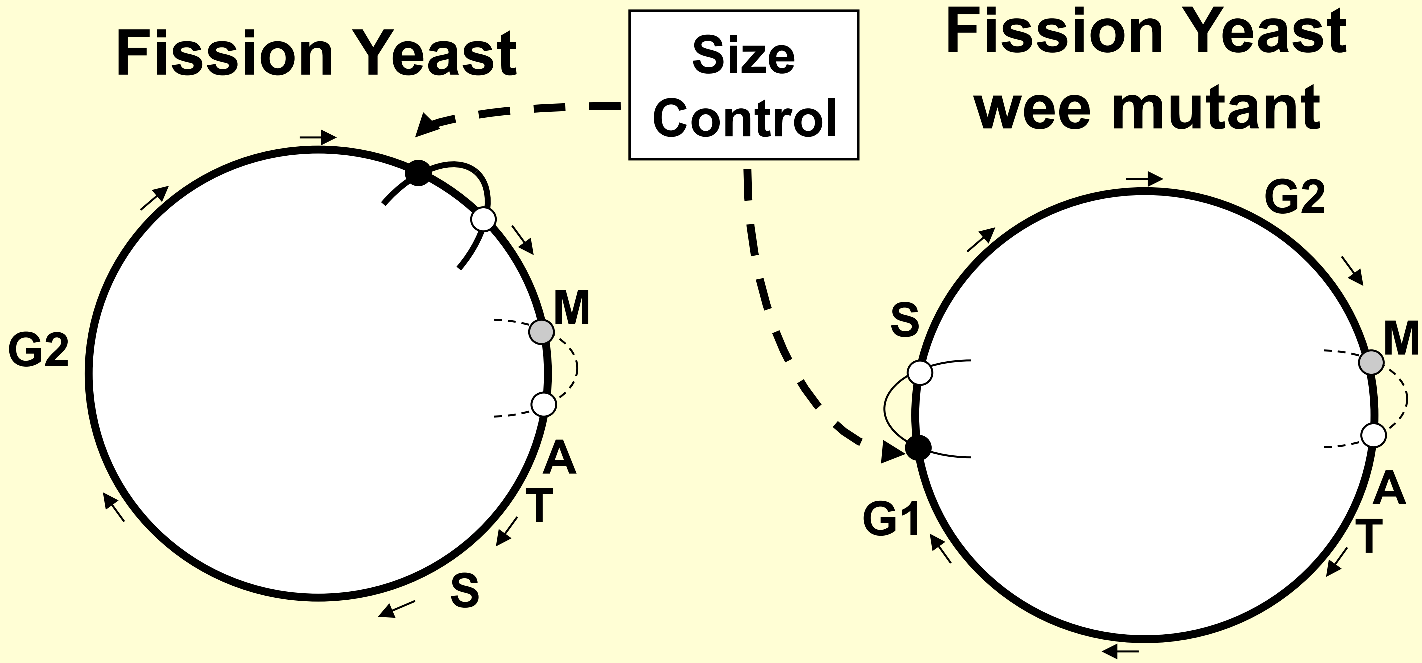


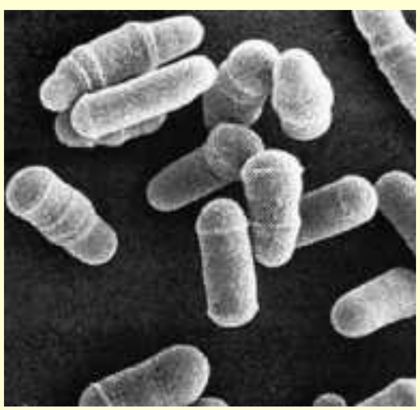
Diversity of Cell Cycle Organization

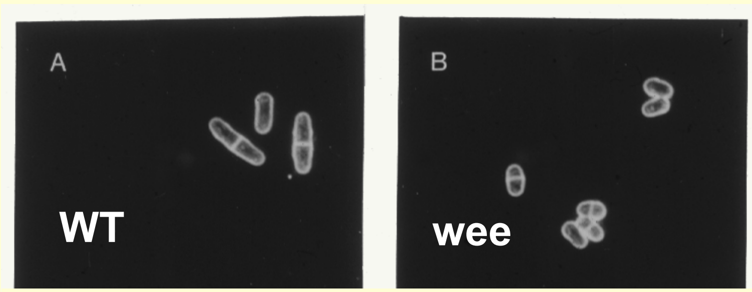




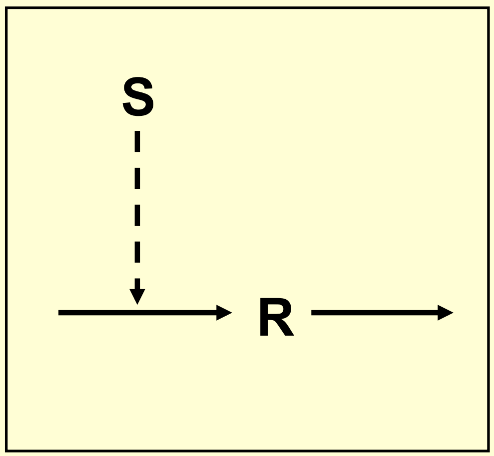
Diversity of Cell Cycle Organization

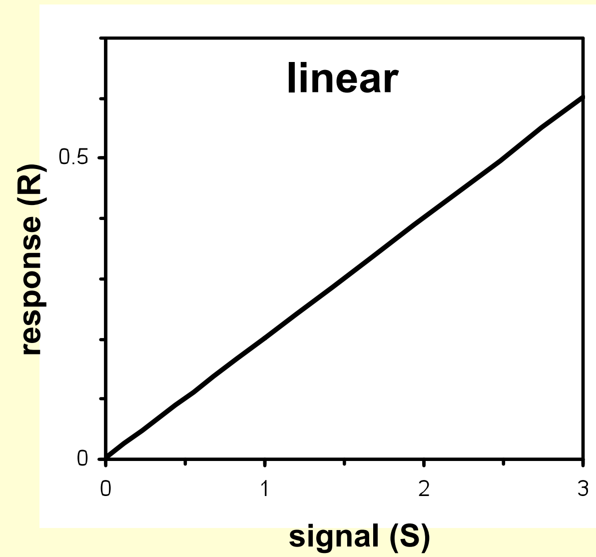






Gene Expression



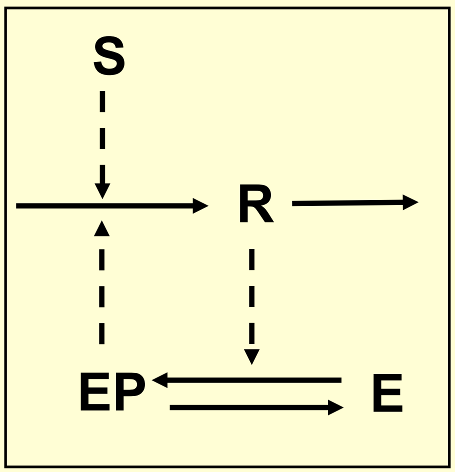


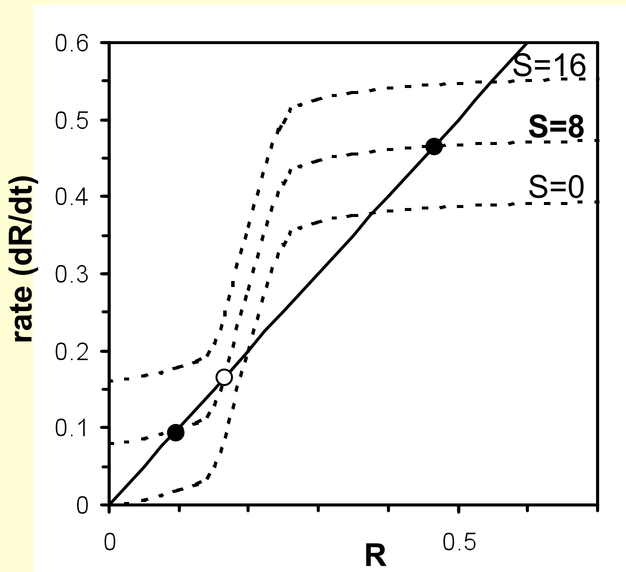
Signal-Response
Curve

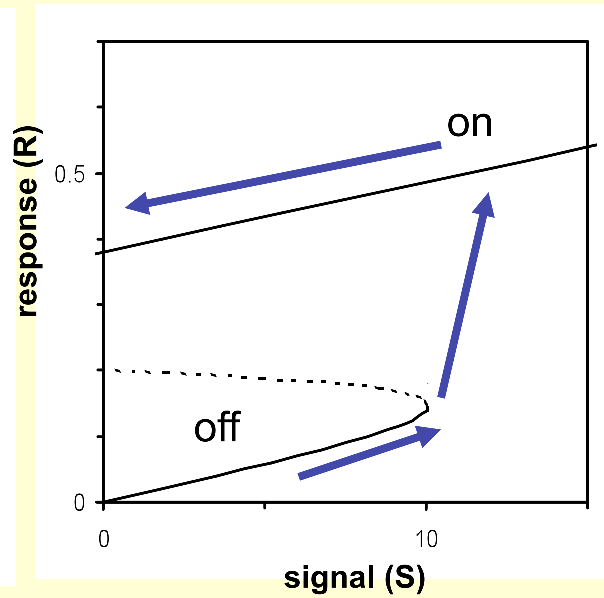
$$\frac{\mathrm{d}R}{\mathrm{d}t} = k_1 S - k_2 R = 0$$

$$R_{ss} = \frac{k_1 S}{k_2}$$

Protein Synthesis: Positive Feedback



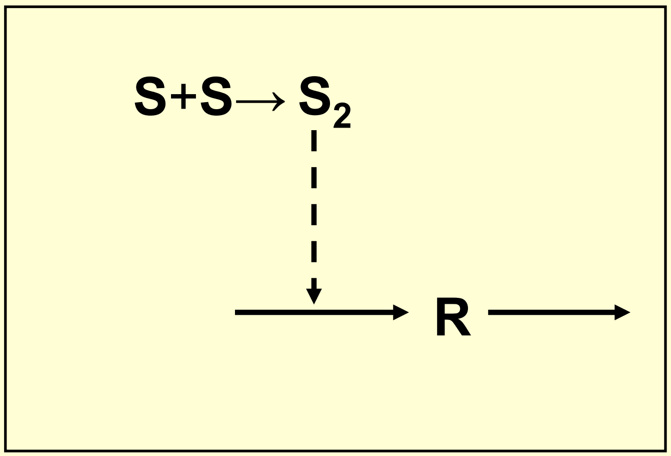


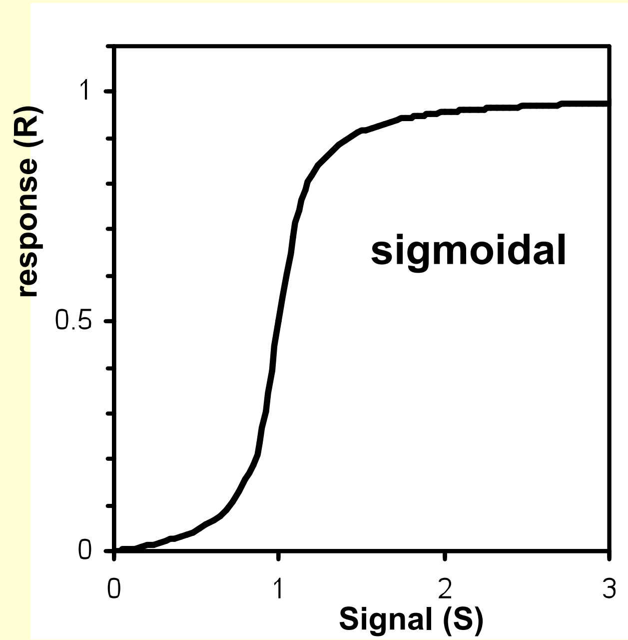


Bistability

Griffith, J Theor Biol (1968)

Cooperative Binding

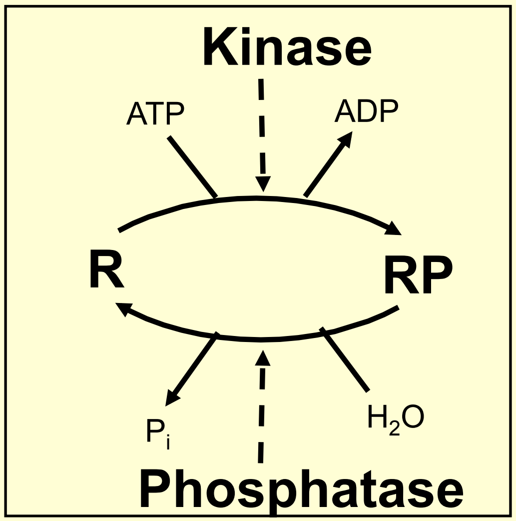


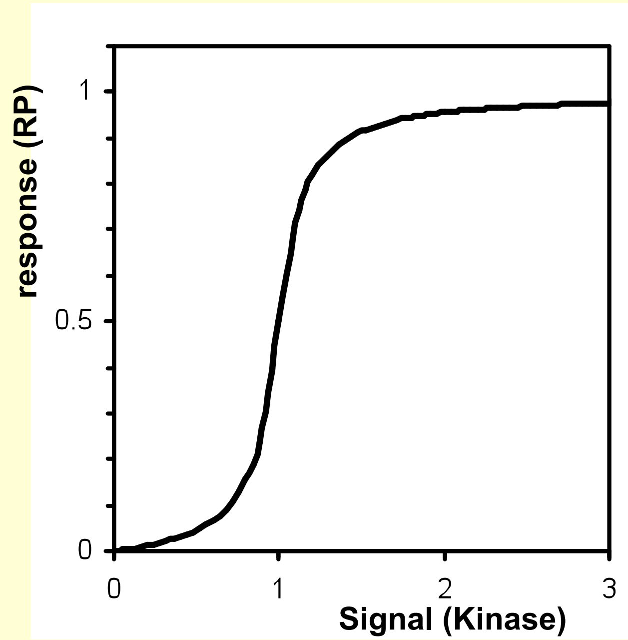


$$\frac{\mathrm{d}R}{\mathrm{d}t} = \frac{k_1 S^2}{K_d^2 + S^2} - k_2 R = 0$$

$$R_{\mathrm{ss}} = \frac{k_1}{k_2} \frac{S^2}{K_d^2 + S^2}$$

Protein Phosphorylation

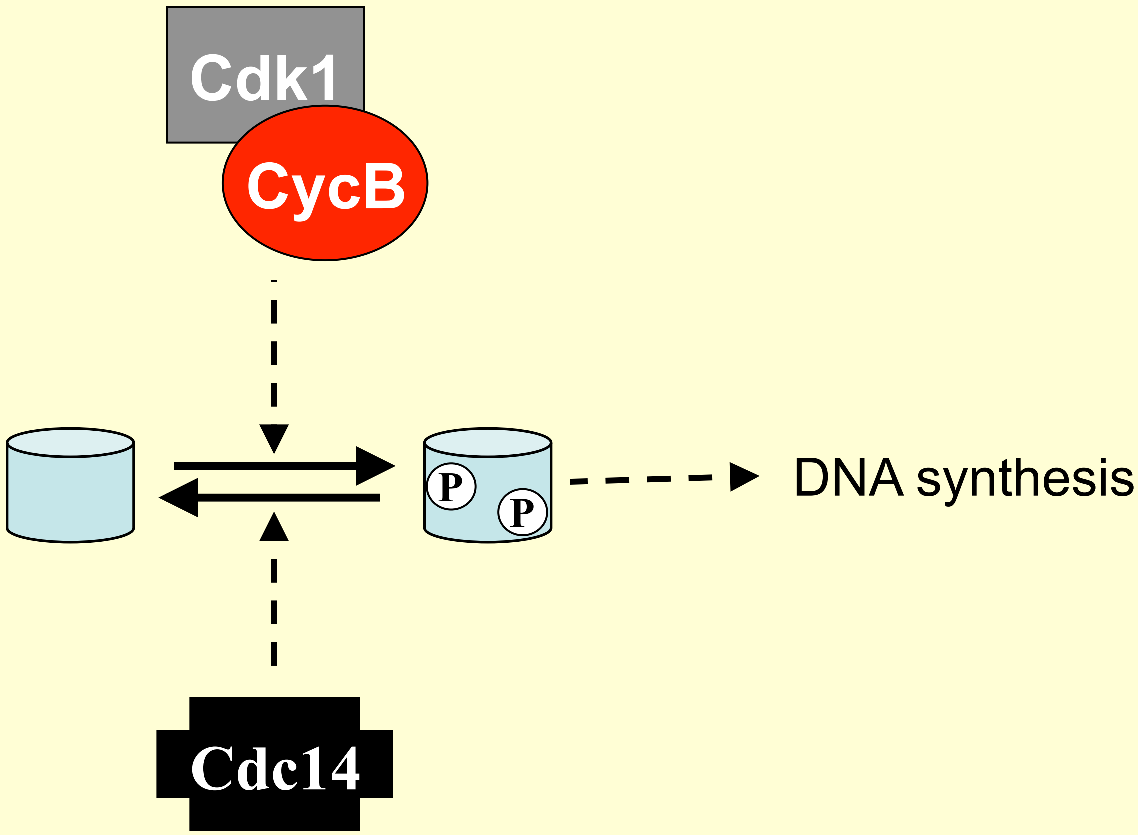




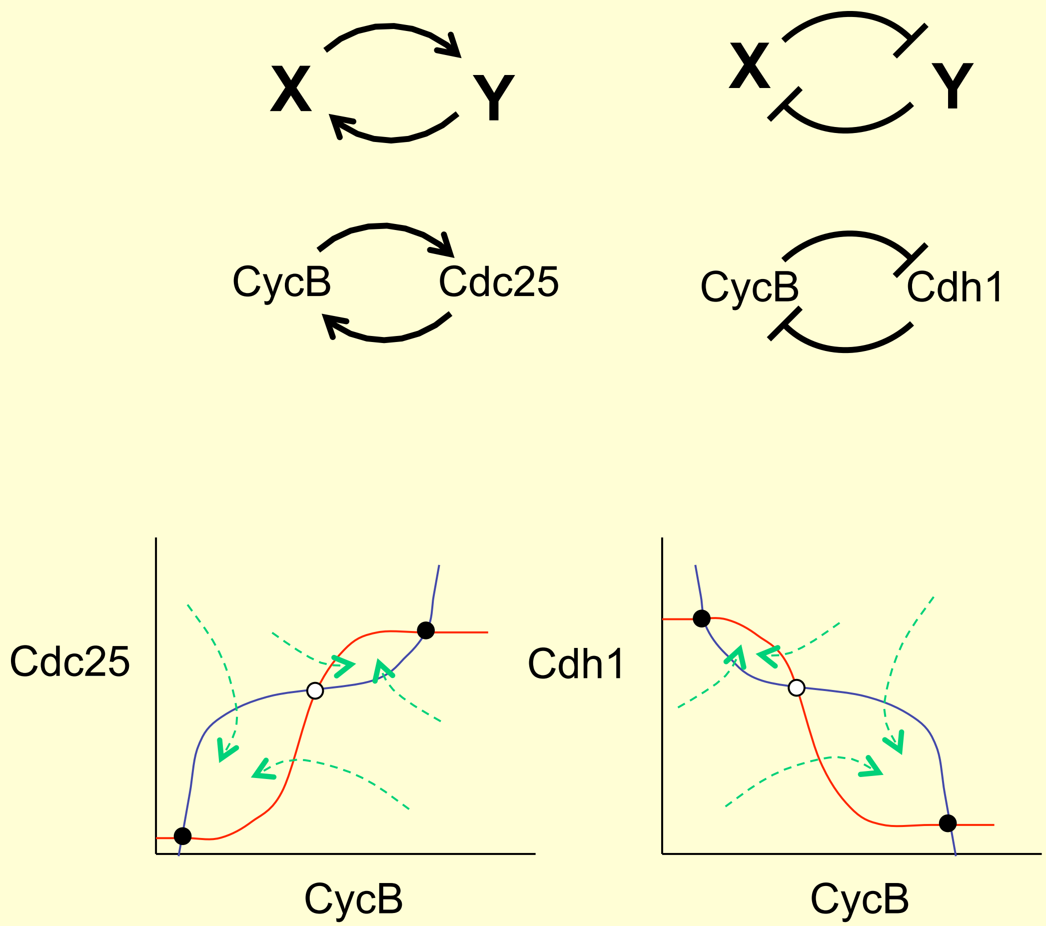
$$\frac{dR_P}{dt} = \frac{k_1 S(R_T - R_P)}{K_{m1} + R_T - R_P} - \frac{k_2 R_P}{K_{m2} + R_P} = 0$$

Goldbeter & Koshland, PNAS (1981)

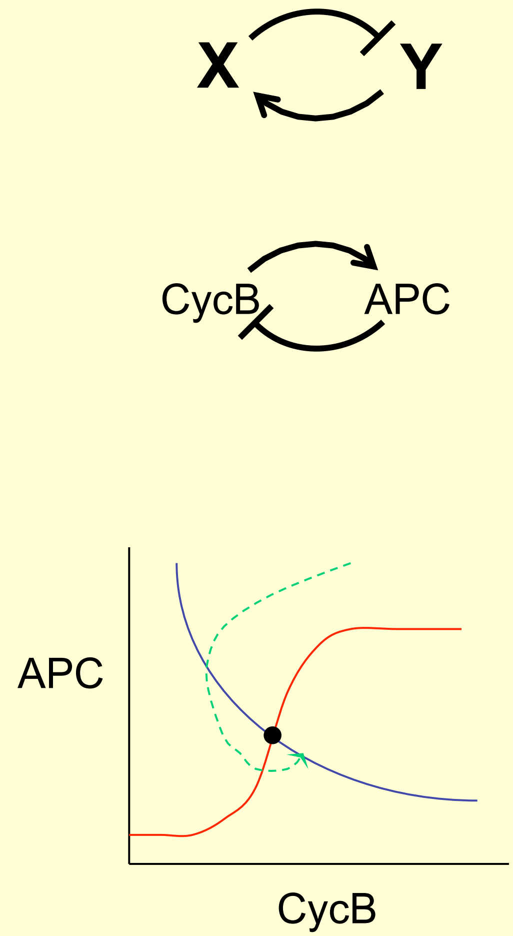
Universal Control Mechanism for the Eukaryotic Cell Cycle

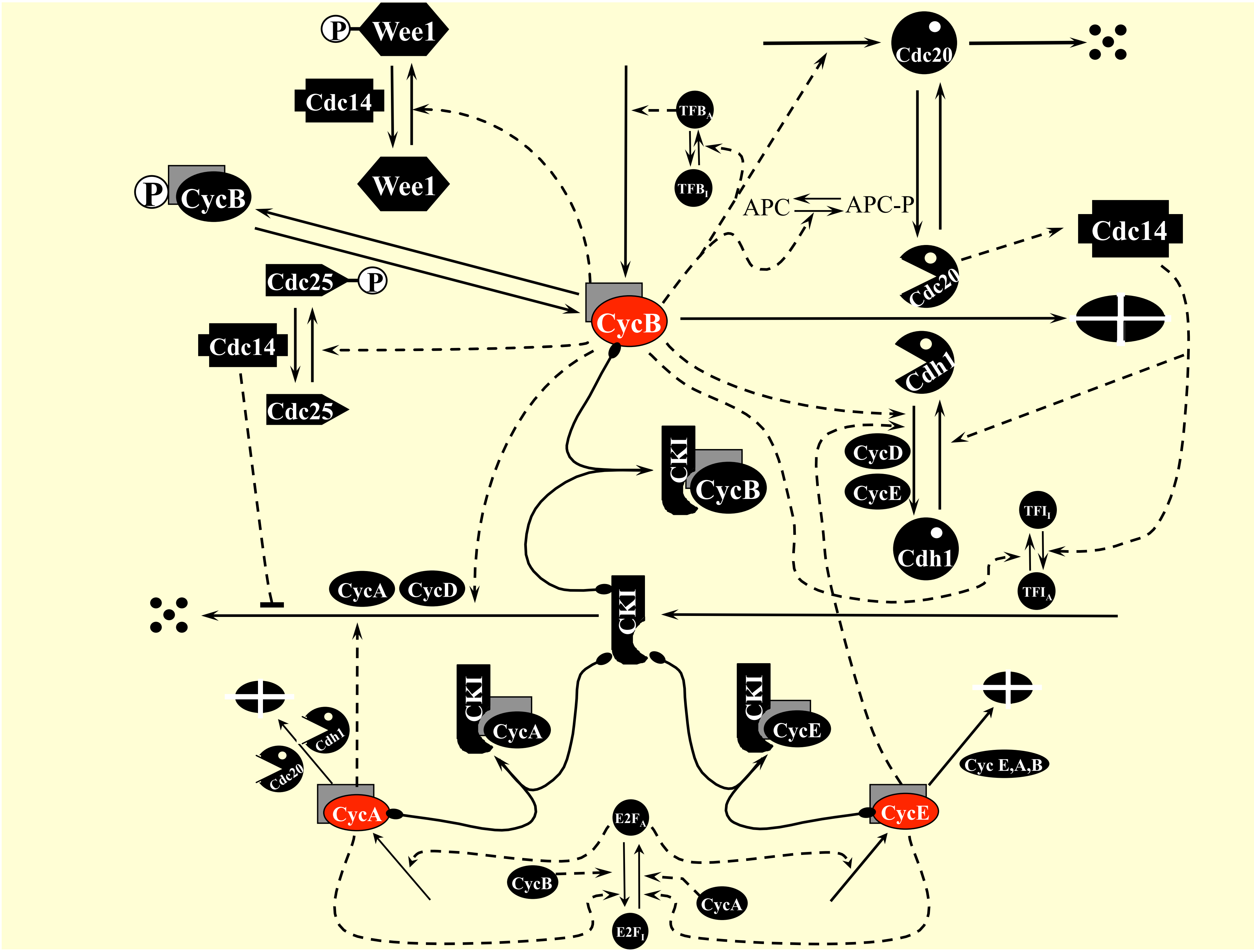


Toggle Switches

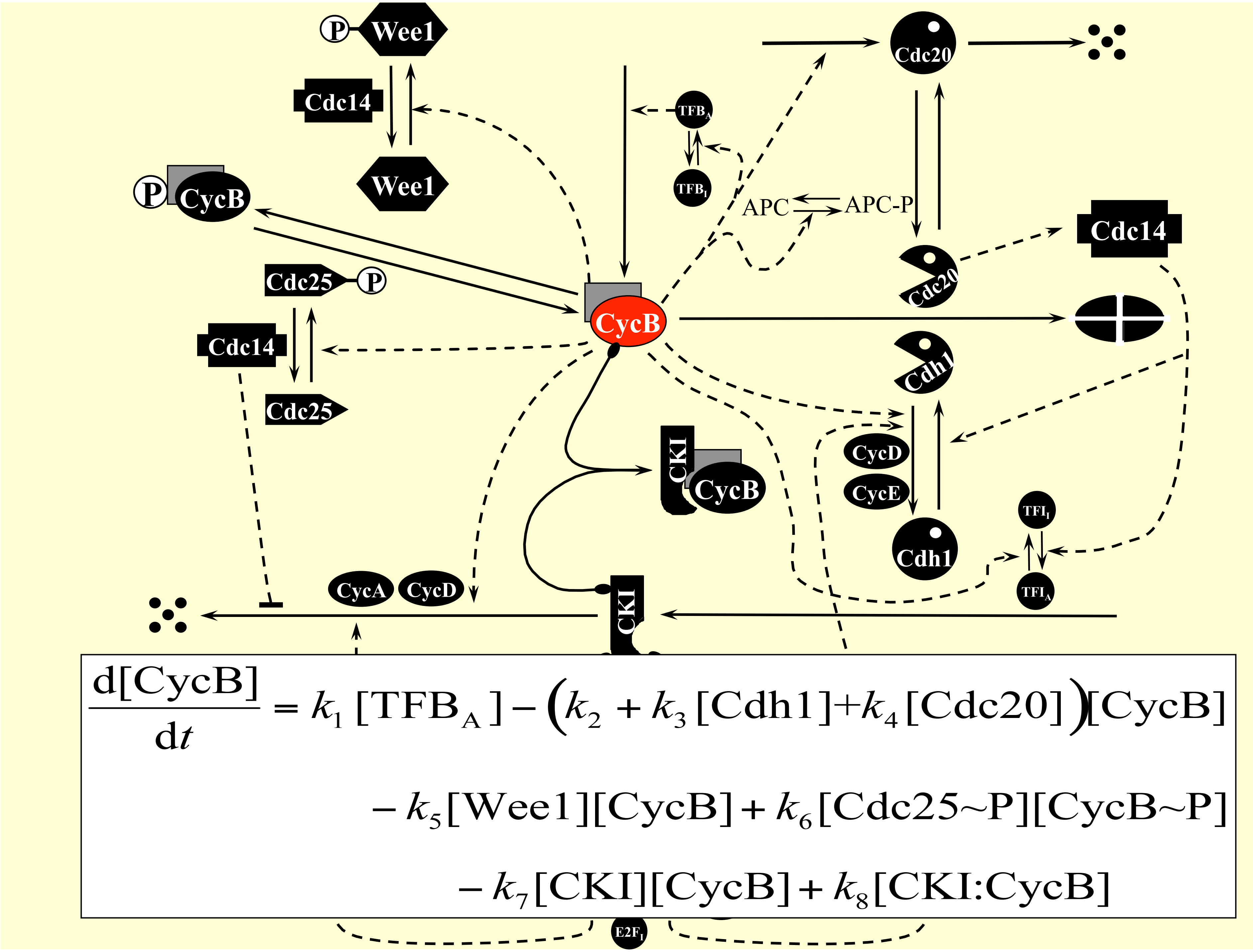


Homeostasis





P
Wee1
Cdc14
Wee1
P
CycB
TFB_A
TFB_I
Cdc20
APC
APC-P
Cdc20
Cdc14
Cdc25
P
Cdc14
CycB
Cdc25
Cdh1
CKI
CycB
CycD
CycE
Cdh1
TFI_I
TFI_A
CycA
CycD
CKI
CKI
CycA
CKI
CycE
Cdh1
Cdc20
Cyc E,A,B
CycA
CycE
E2F_A
CycB
CycA
E2F_I

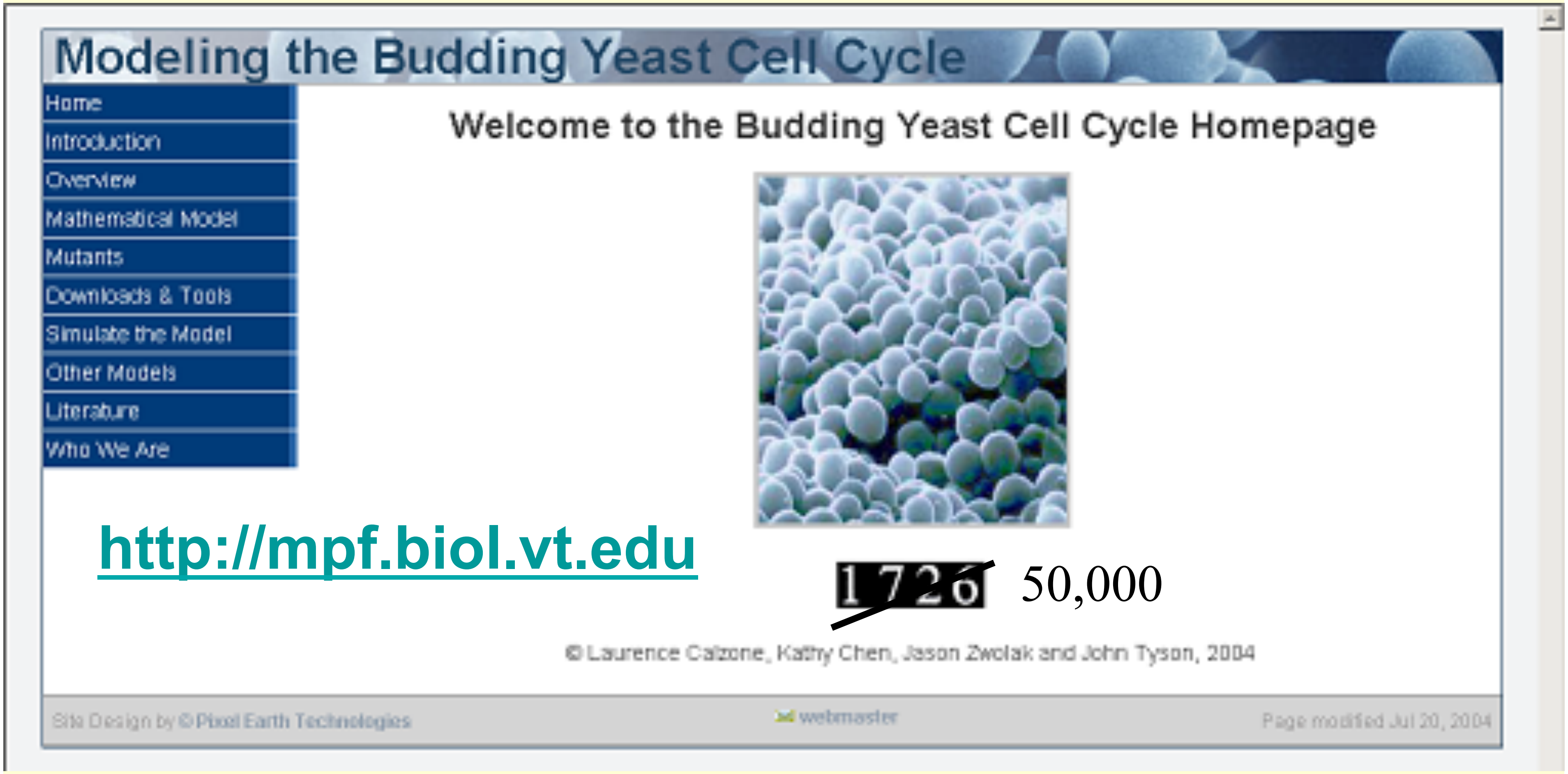


$$\frac{d[\mathrm{CycB}]}{dt} = k_1[\mathrm{TFB_A}] - \left(k_2 + k_3[\mathrm{Cdh1}] + k_4[\mathrm{Cdc20}]\right)[\mathrm{CycB}]$$

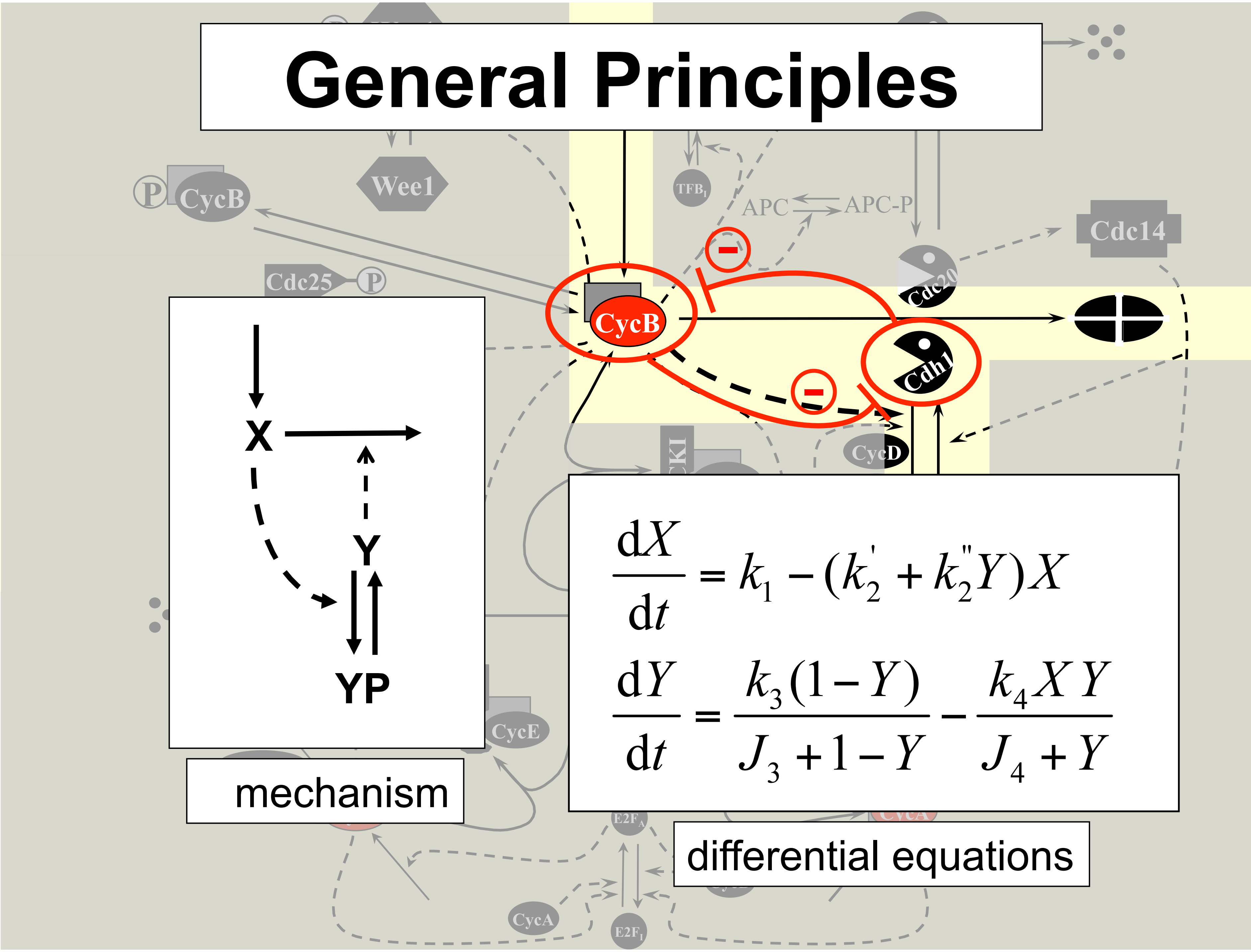
$$- k_5[\mathrm{Wee1}][\mathrm{CycB}] + k_6[\mathrm{Cdc25{\sim}P}][\mathrm{CycB{\sim}P}]$$

$$- k_7[\mathrm{CKI}][\mathrm{CycB}] + k_8[\mathrm{CKI{:}CycB}]$$

Detailed Simulations



General Principles

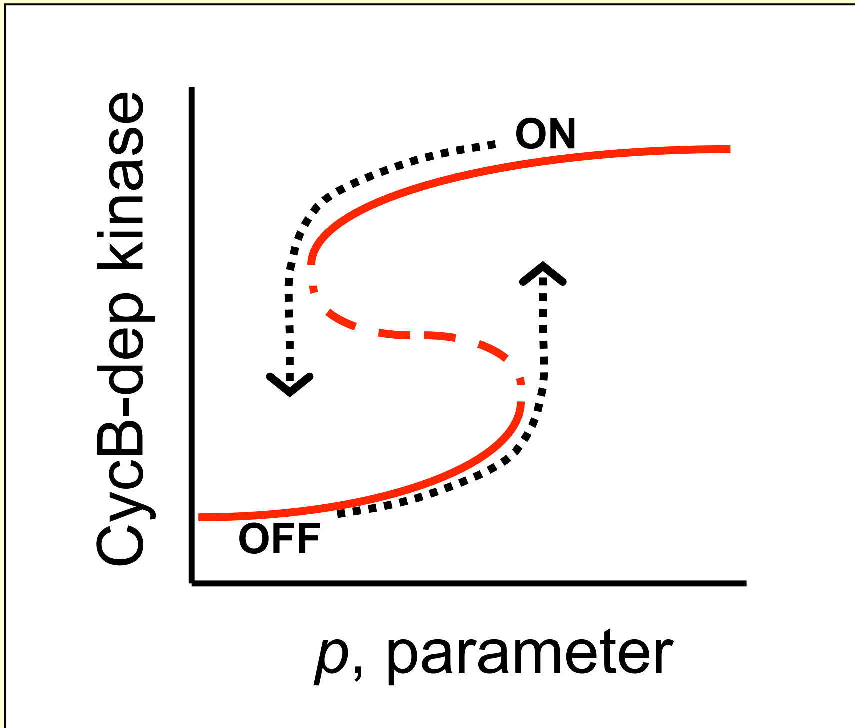


mechanism

$$\frac{dX}{dt} = k_1 - (k_2^{'} + k_2^{''} Y) X$$

$$\frac{dY}{dt} = \frac{k_3(1-Y)}{J_3 + 1 - Y} - \frac{k_4 X Y}{J_4 + Y}$$

differential equations

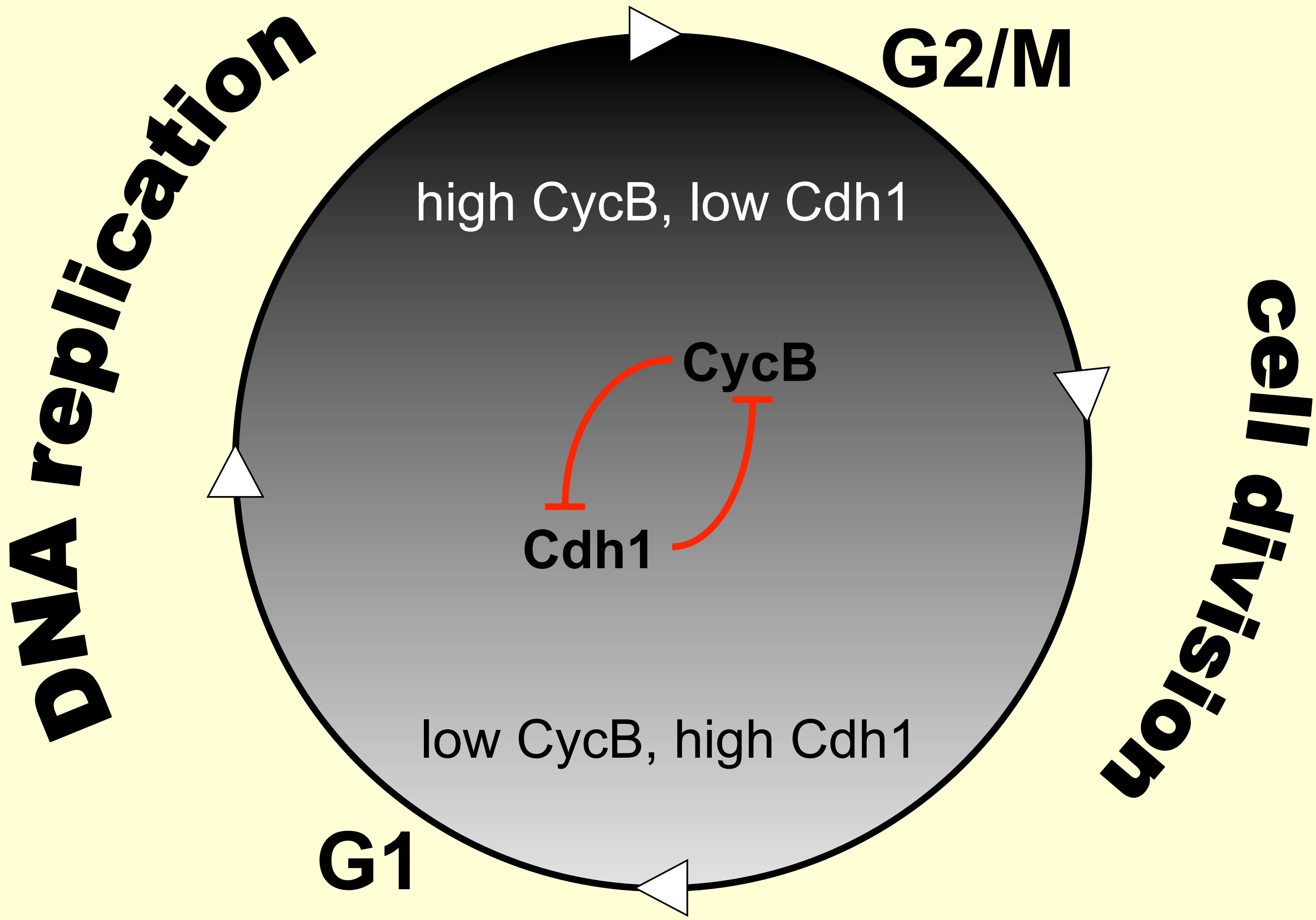


$$\frac{dX}{dt} = k_1 S - (k_1' + k_2'' Y) X$$

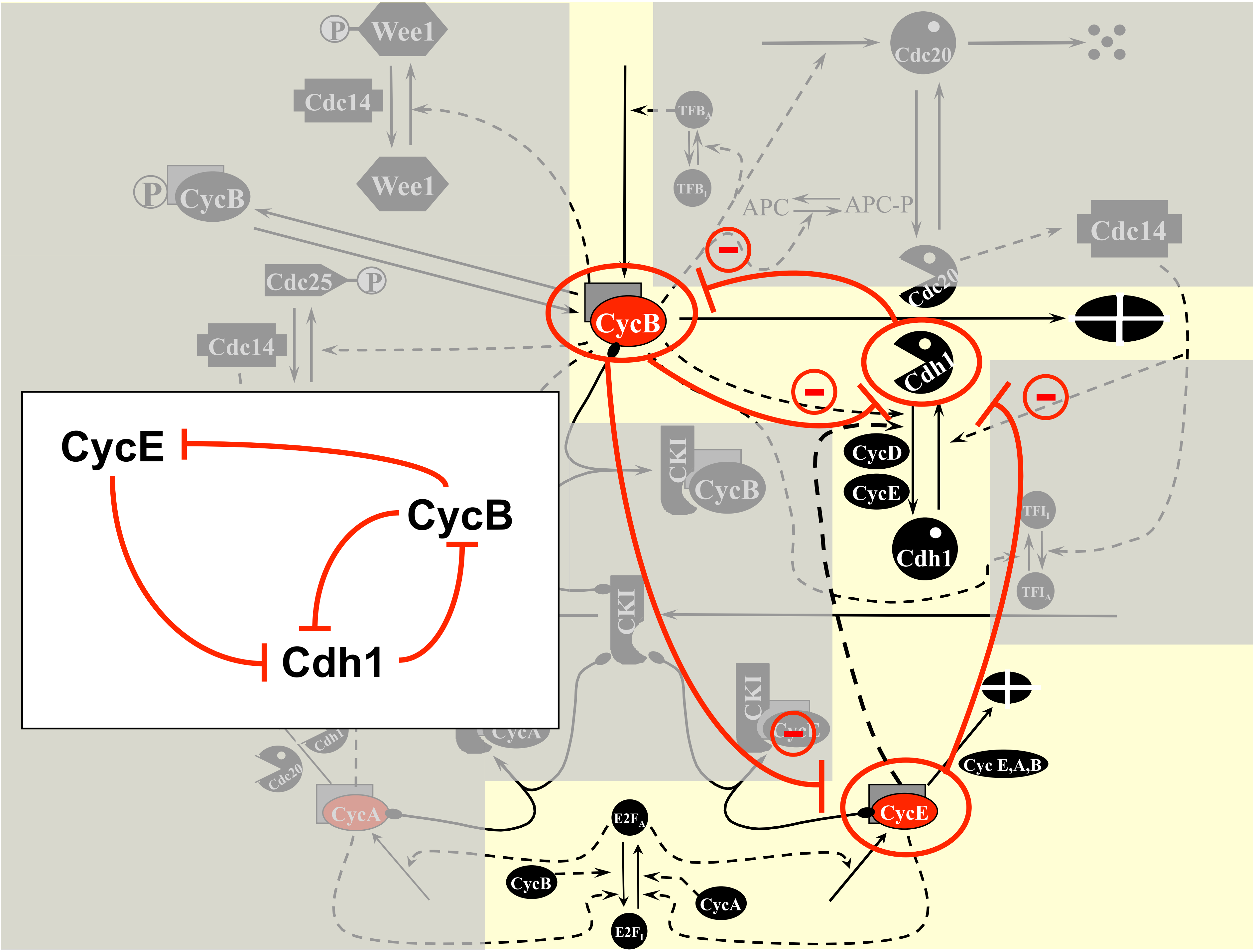
$$\frac{dY}{dt} = \frac{k_3 A (1-Y)}{J_3 + 1 - Y} - \frac{k_4 X Y}{J_4 + Y}$$

differential equations

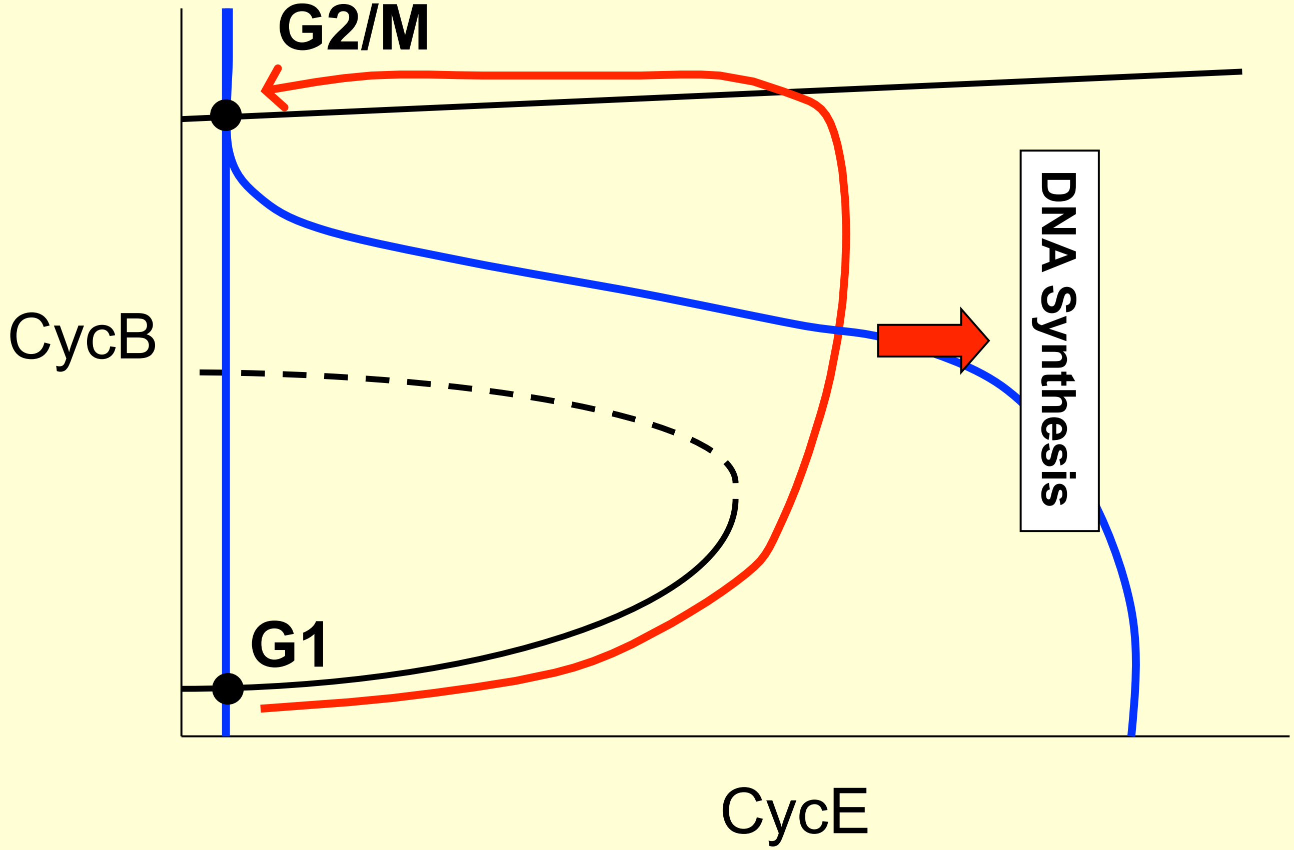
Cell Cycle Regulation

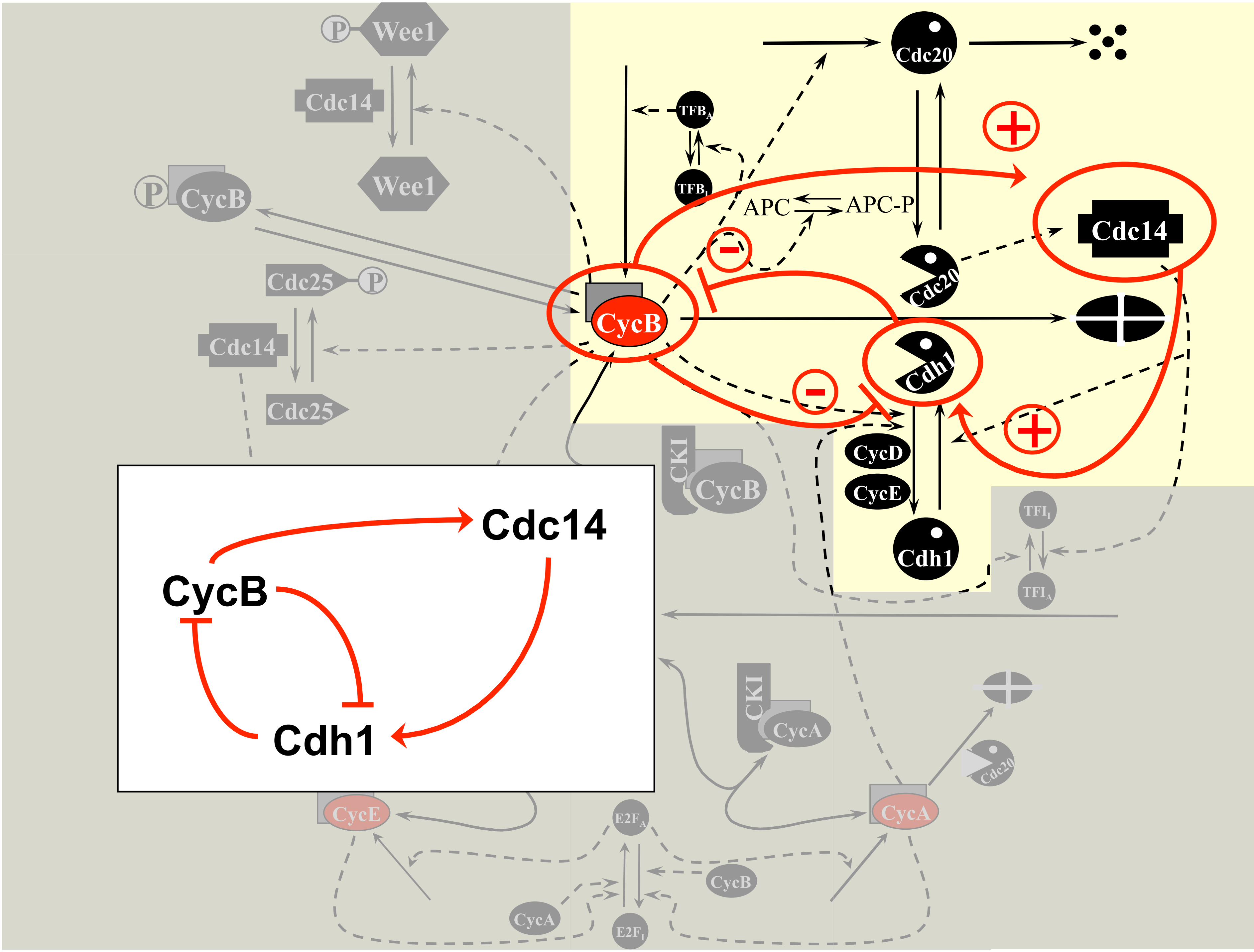


What mechanisms flip the switch up and down?

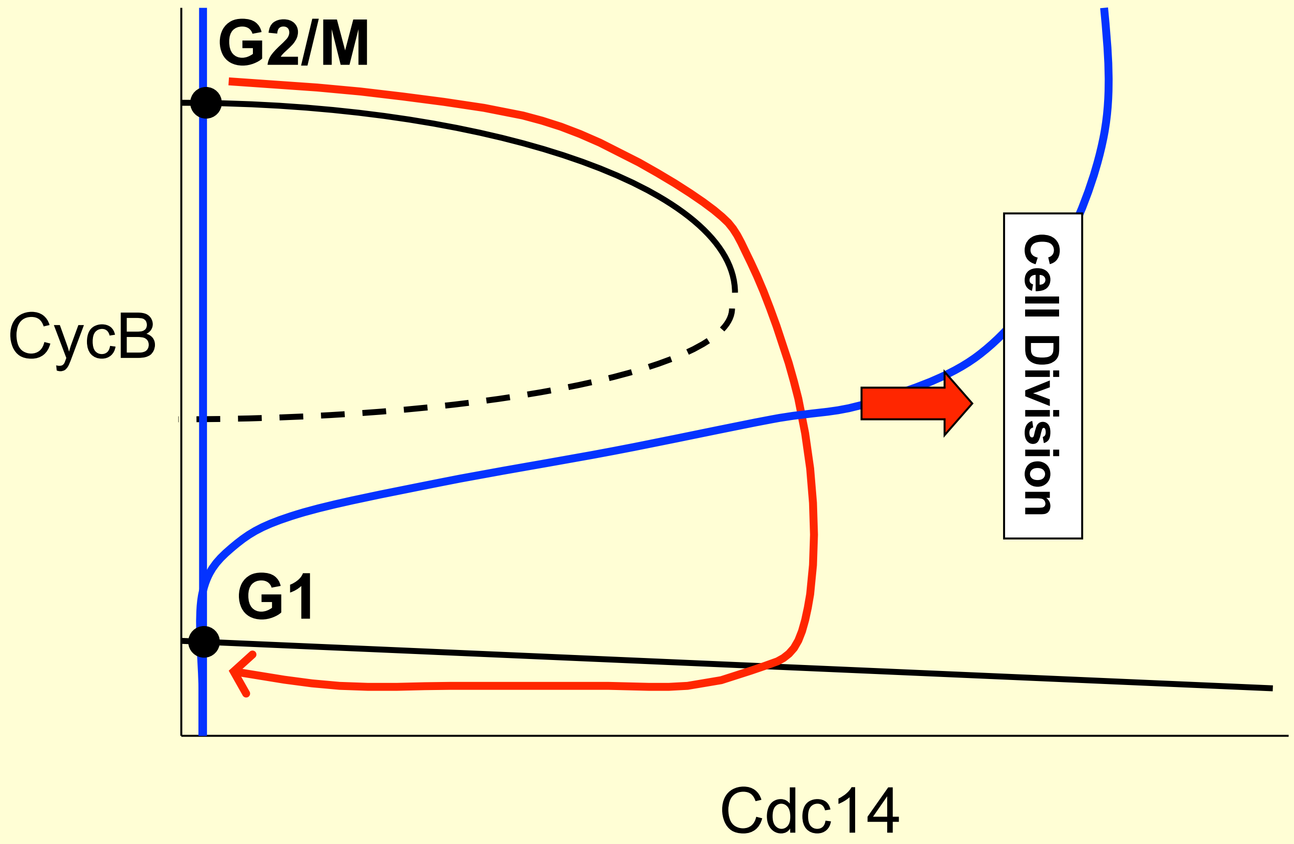

CycE
CycB
Cdh1
Wee1
Cdc14
Cdc20
TFB
APC
APC-P
Cdc25
CKI
CycD
CycA
TFI
E2F
Cyc E,A,B

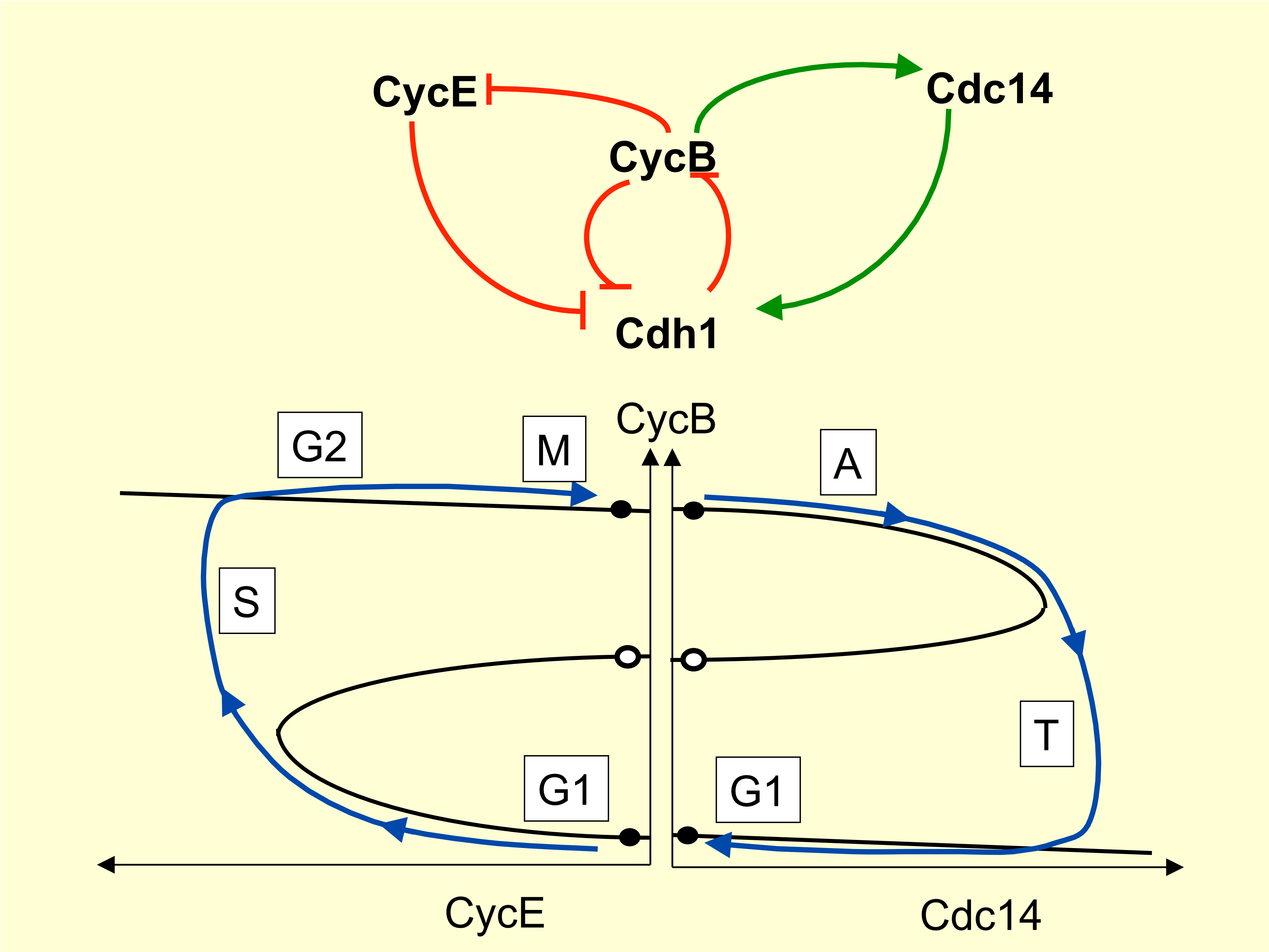
Entry

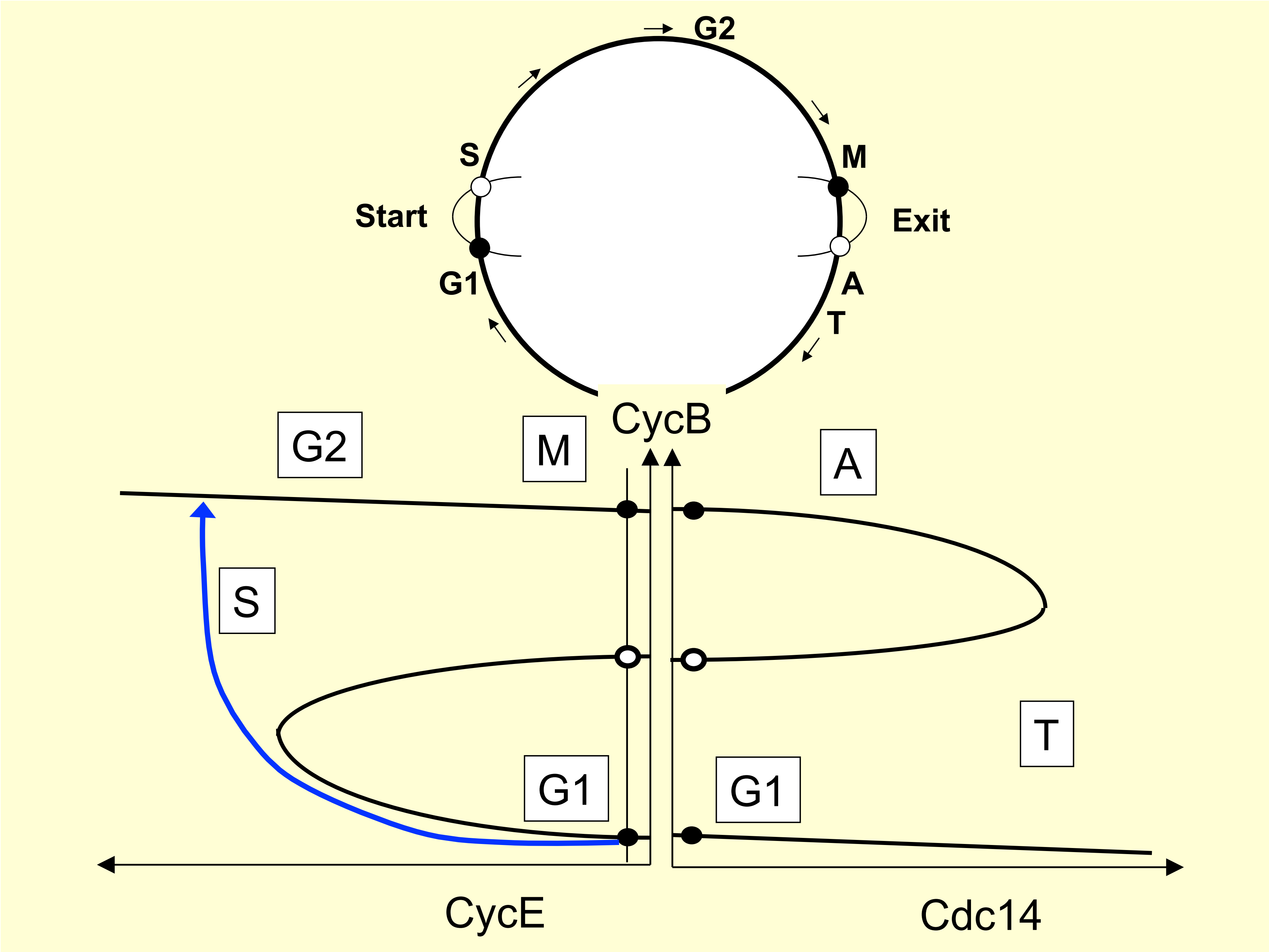


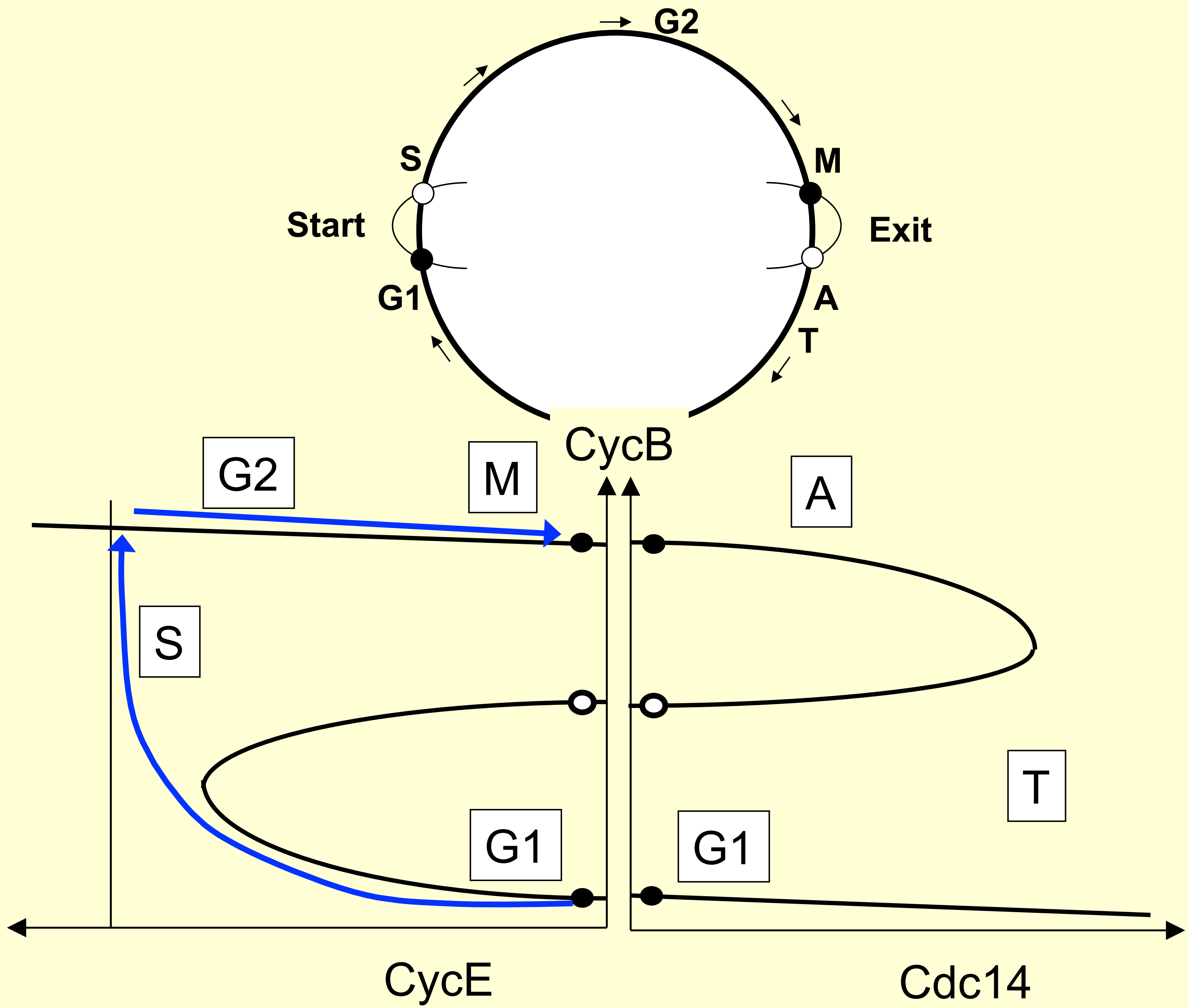

P
Wee1
Cdc14
Wee1
P
CycB
Cdc25
P
Cdc14
Cdc25
TFB_A
TFB_I
APC
APC-P
Cdc20
Cdc20
Cdc14
CycB
Cdh1
CycD
CycE
Cdh1
CKI
CycB
TFI_I
TFI_A
CycB
Cdc14
Cdh1
CKI
CycA
CycE
E2F_A
CycA
Cdc20
CycB
CycA
E2F_I

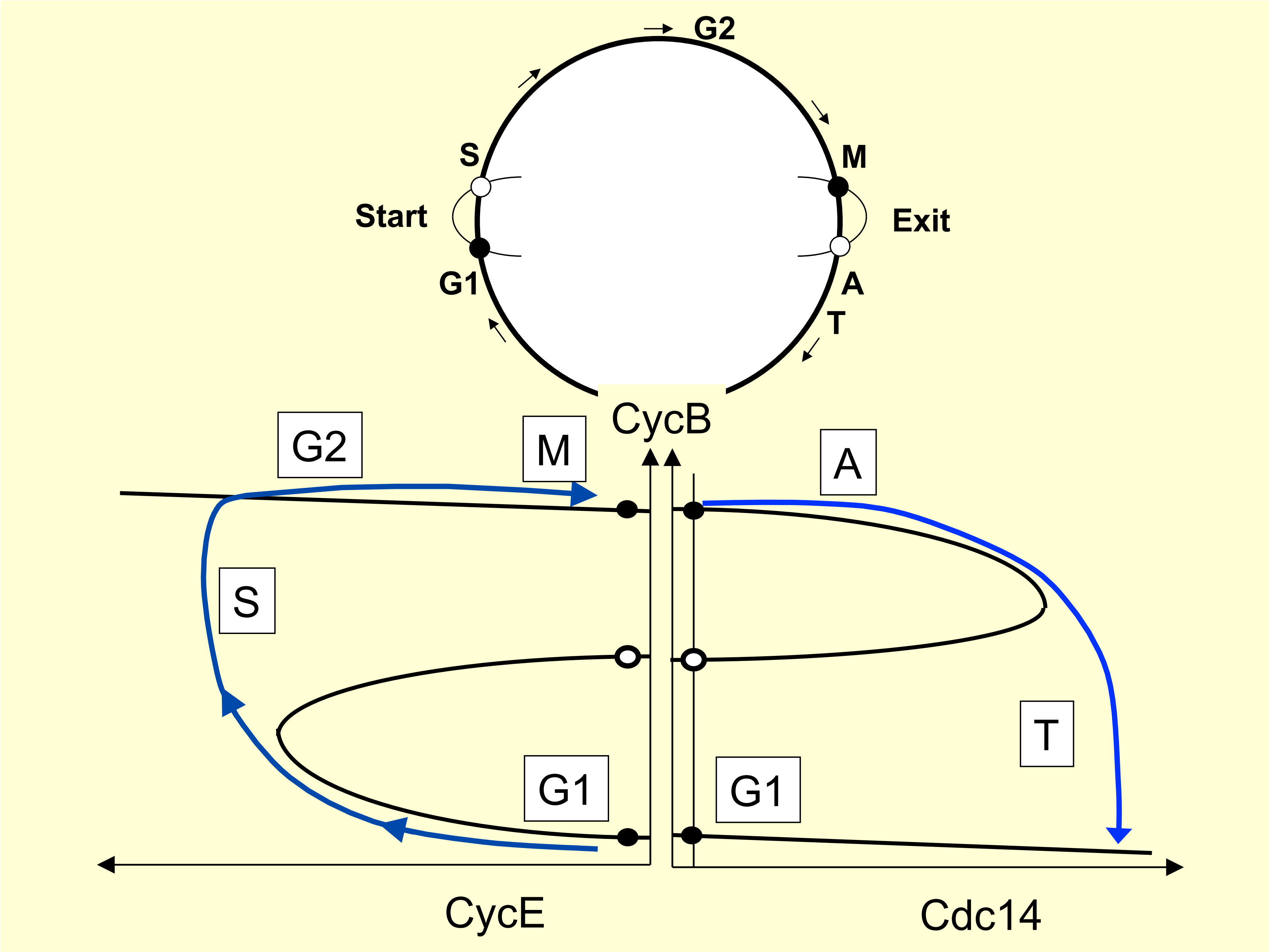
Exit

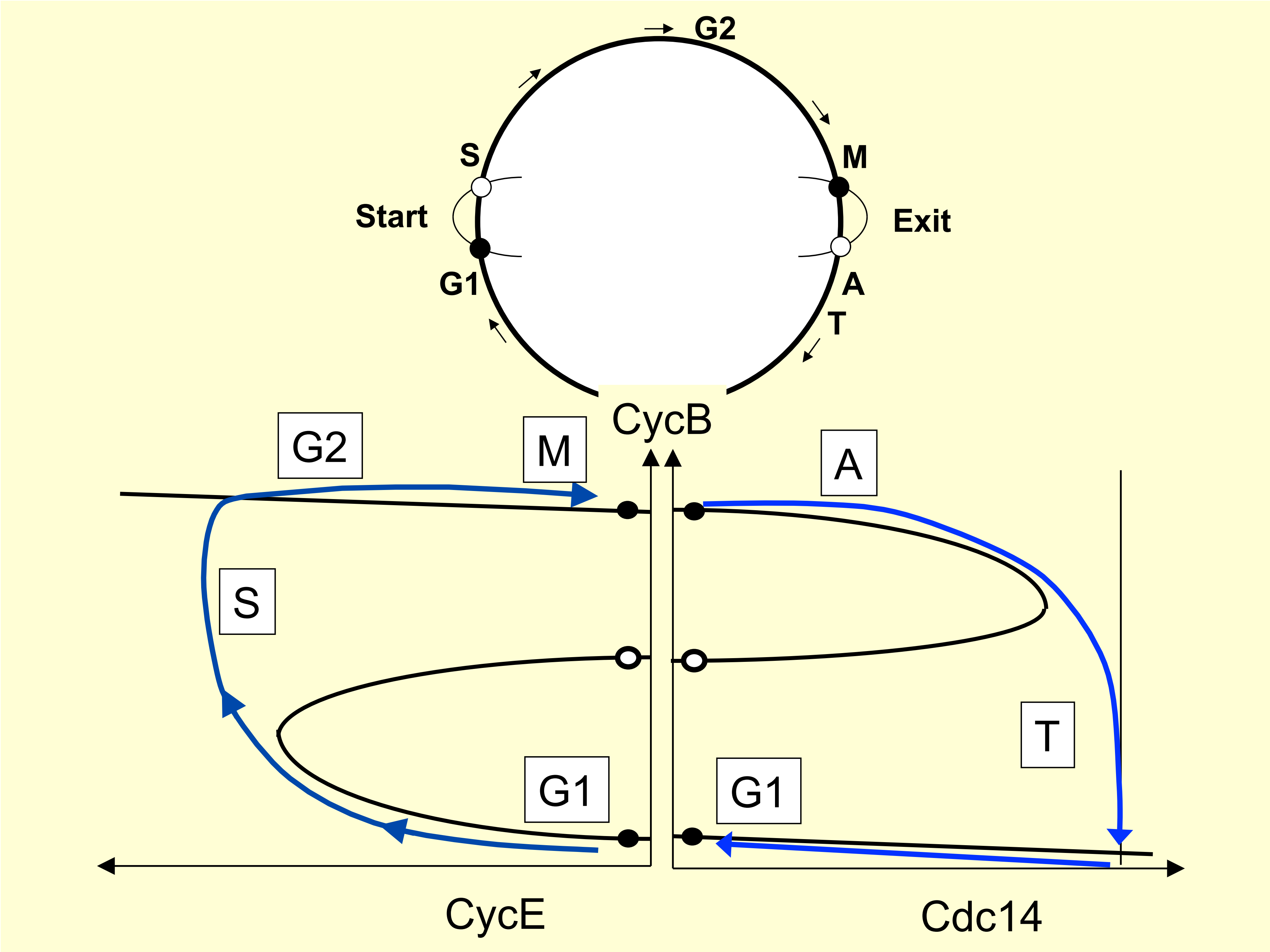


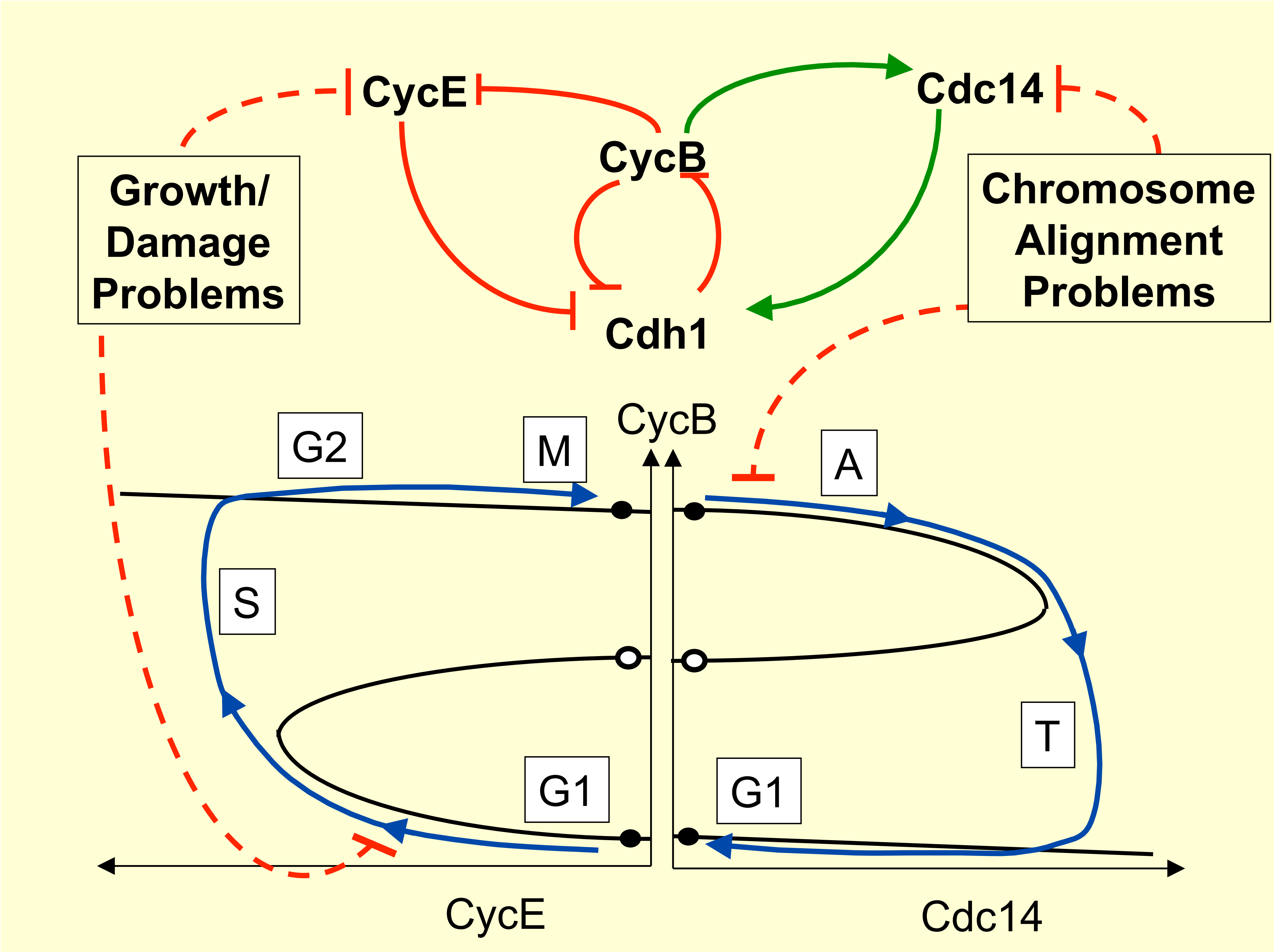

CycE
Cdc14
CycB
Cdh1
CycB
G2
M
A
S
T
G1
G1
CycE
Cdc14


G2
S
Start
G1
M
Exit
A
T
CycB
G2
M
A
S
T
G1
G1
CycE
Cdc14


G2
S
Start
G1
M
Exit
A
T
CycB
G2
M
A
S
T
G1
G1
CycE
Cdc14


G2
S
Start
G1
M
Exit
A
T
CycB
G2
M
A
S
T
G1
G1
CycE
Cdc14


G2
S
M
Start
Exit
G1
A
T
CycB
G2
M
A
S
T
G1
G1
CycE
Cdc14



CycE
Cdc14
CycB
Growth/
Damage
Problems
Chromosome
Alignment
Problems
Cdh1
CycB
G2
M
A
S
T
G1
G1
CycE
Cdc14