系统生物学

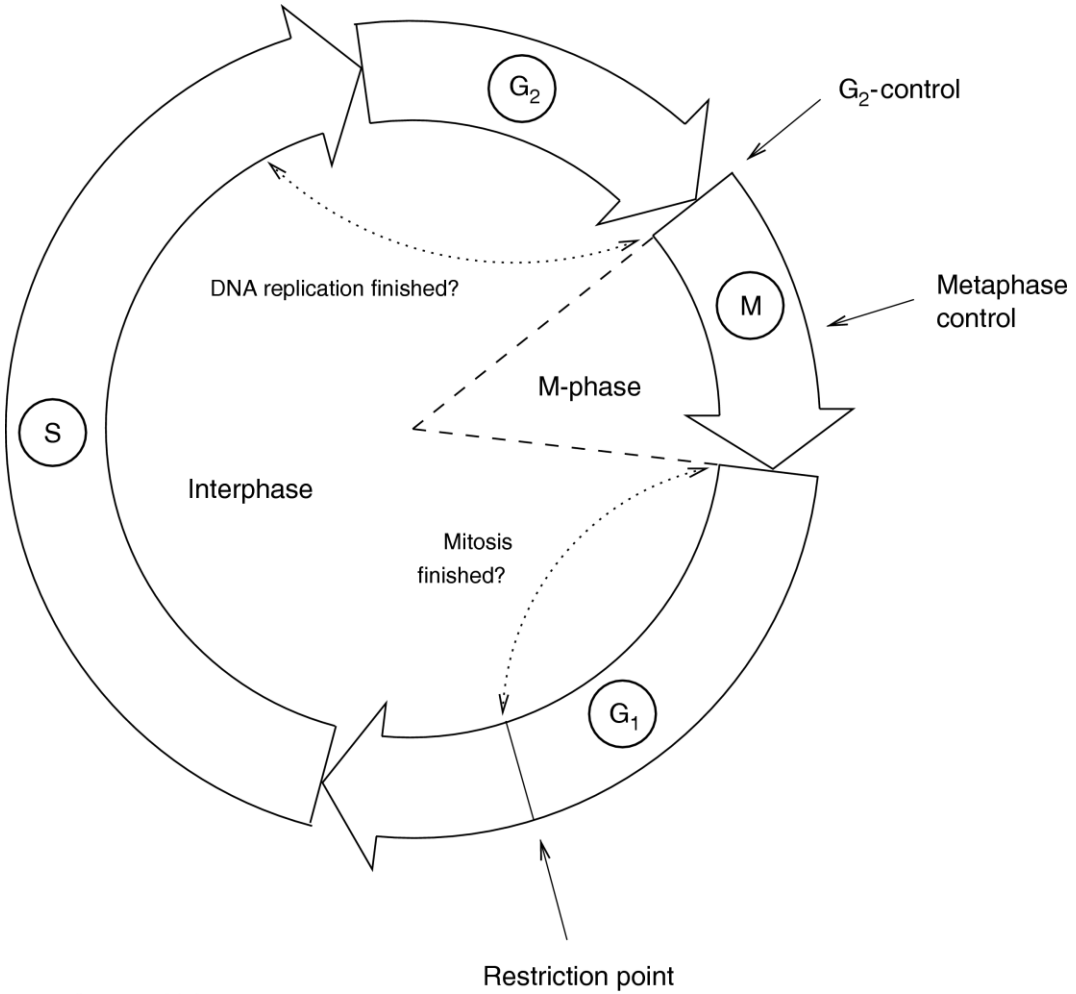
(Systems Biology)

马彬广

细胞行为建模

（第十六讲）

细胞循环



Steps in the cycle

- G1 cyclin rises, bind to their CDK, signal the cell to prepare the chromosome replication

- S phase promoting factor (SPF) rises, cyclin A with CDK2, enters nucleus and prepares the cell to duplicate its DNA.

- As DNA replication continues, cyclin E is destroyed and mitotic cyclin increase (in G2)

- The M phase-promoting factor (the complex of mitotic cyclins with the M-phase CDK) initiates (i) assembly of the mitotic spindle; (2) breakdown of the nuclear envelope; (iii) condensation of the chromosomes.

- Into metaphase, the M phase-promoting factor activate anaphase-promoting complex (APC) which allows the sister chromatids at the metaphase to separate and move to the poles (anaphase), thereby completing mitosis.

- APC destroys mitotic cyclin and turns on the synthesis of G1 cyclin for the next cycle.

Minimal Cascade model of a Mitotic Oscillator

- In yeast, the CDKs have been identified, as cdc2 kinase in fission yeast, and cdc28 kinase in budding yeast.

- The minimal model was proposed by Goldbeter (Goldbeter A. PNAS 1991, 88: 9107-9111).

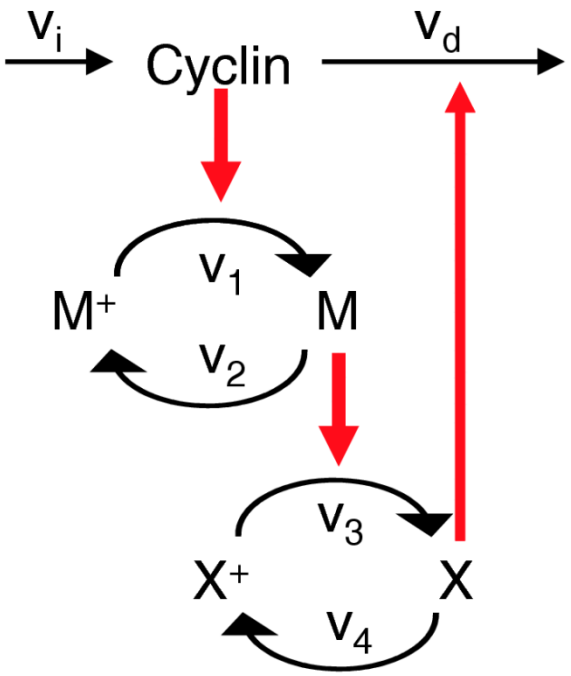
- It is a bicyclic cascade model involving phosphorylation and dephosphorylation.

- The model was used to test the hypothesis that cell cycle oscillation may arise from a negative feedback loop, i.e., the cyclin activates the Cdc2 kinase, while the Cdc 2 kinase triggers the degradation of the cyclin.

- See the next page for the model.

细胞周期模型

Bicyclic cascade model of yeast cell cycle



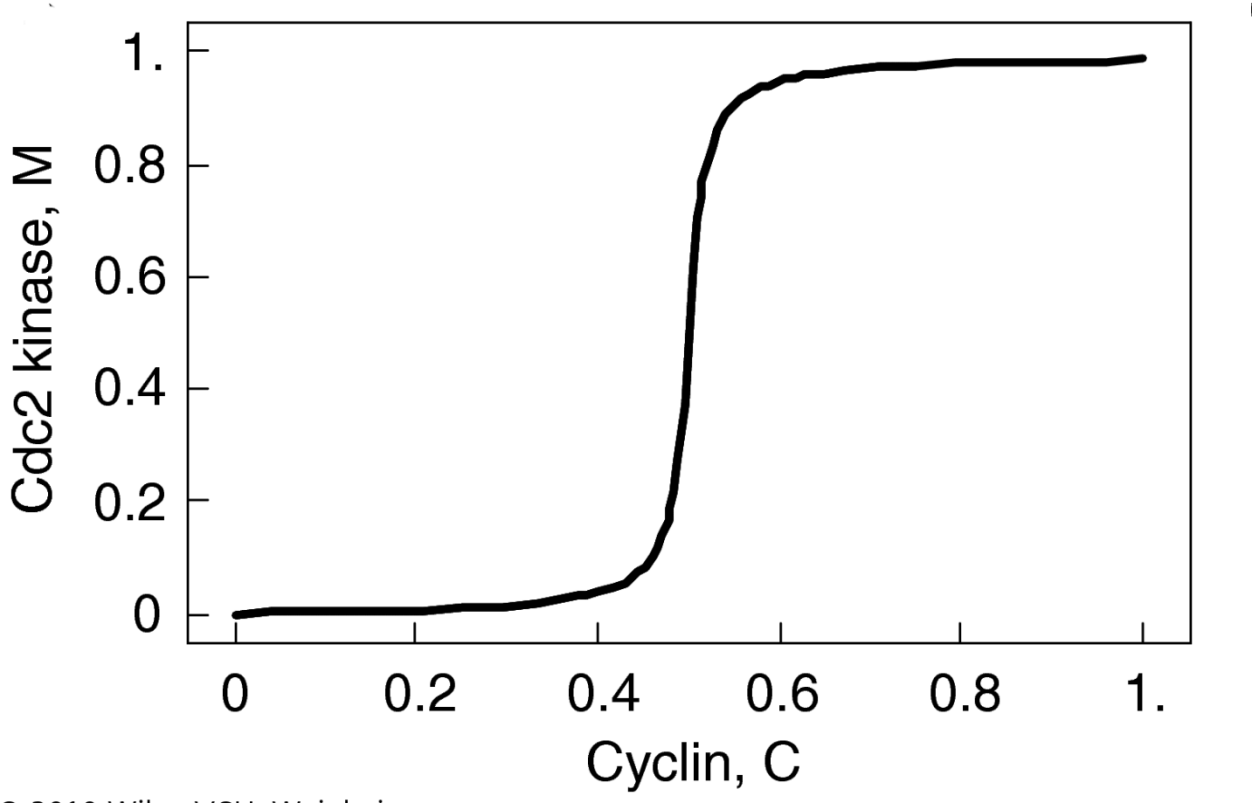
The ODE system

$$\begin{cases} \dfrac{dC}{dt} = v_i - v_d \dfrac{X \cdot C}{K_{md} + C} - k_d C \\ \dfrac{dM}{dt} = \dfrac{V_{m1} \cdot (1 - M)}{K_{m1} + (1 - M)} - \dfrac{V_{m2} \cdot M}{K_{m2} + M} \\ \dfrac{dX}{dt} = \dfrac{V_{m2} \cdot (1 - X)}{K_{m3} + (1 - X)} - \dfrac{V_{m4} \cdot X}{K_{m4} + X} \end{cases}$$

The model comprising cyclin production and degradation, phosphorylation and dephosphorylation of Cdc2 kinase, and phosphorylation and dephosphorylation of the cyclin protease.Parameter values: $K_{mi} = 0.05$ ($i = 1, \ldots, 4$), $K_{mc} = 0.5$, $k_d = 0.01$, $v_i = 0.025$, $v_d = 0.25$, $V_{m1} = 3$, $V_{m2} = 1.5$, $V_{m3} = 1$, $V_{m4} = 0.5$.

细胞周期模型

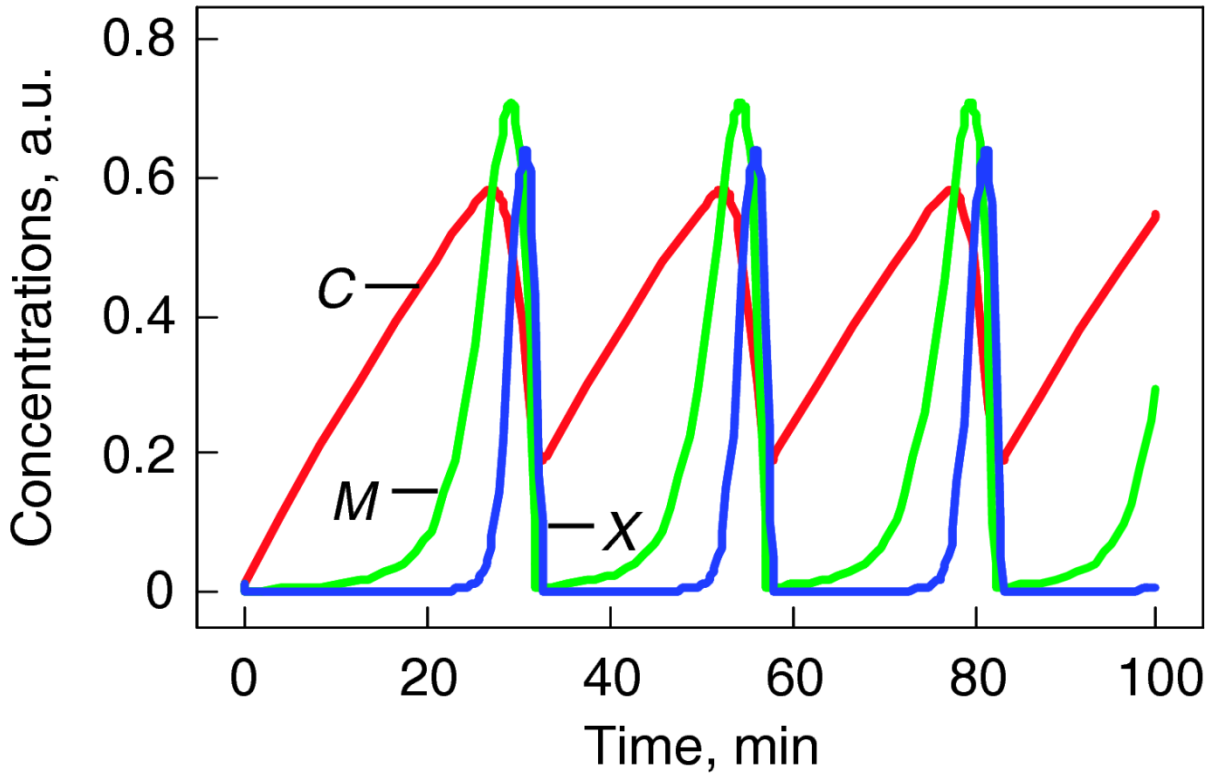
Two thresholds:



Threshold-type dependence of the fractional concentration of active Cdc2 kinase on the cyclin concentration. Initial conditions in are $C(0) = M(0) = X(0) = 0.01$. Units: μM and min−1.

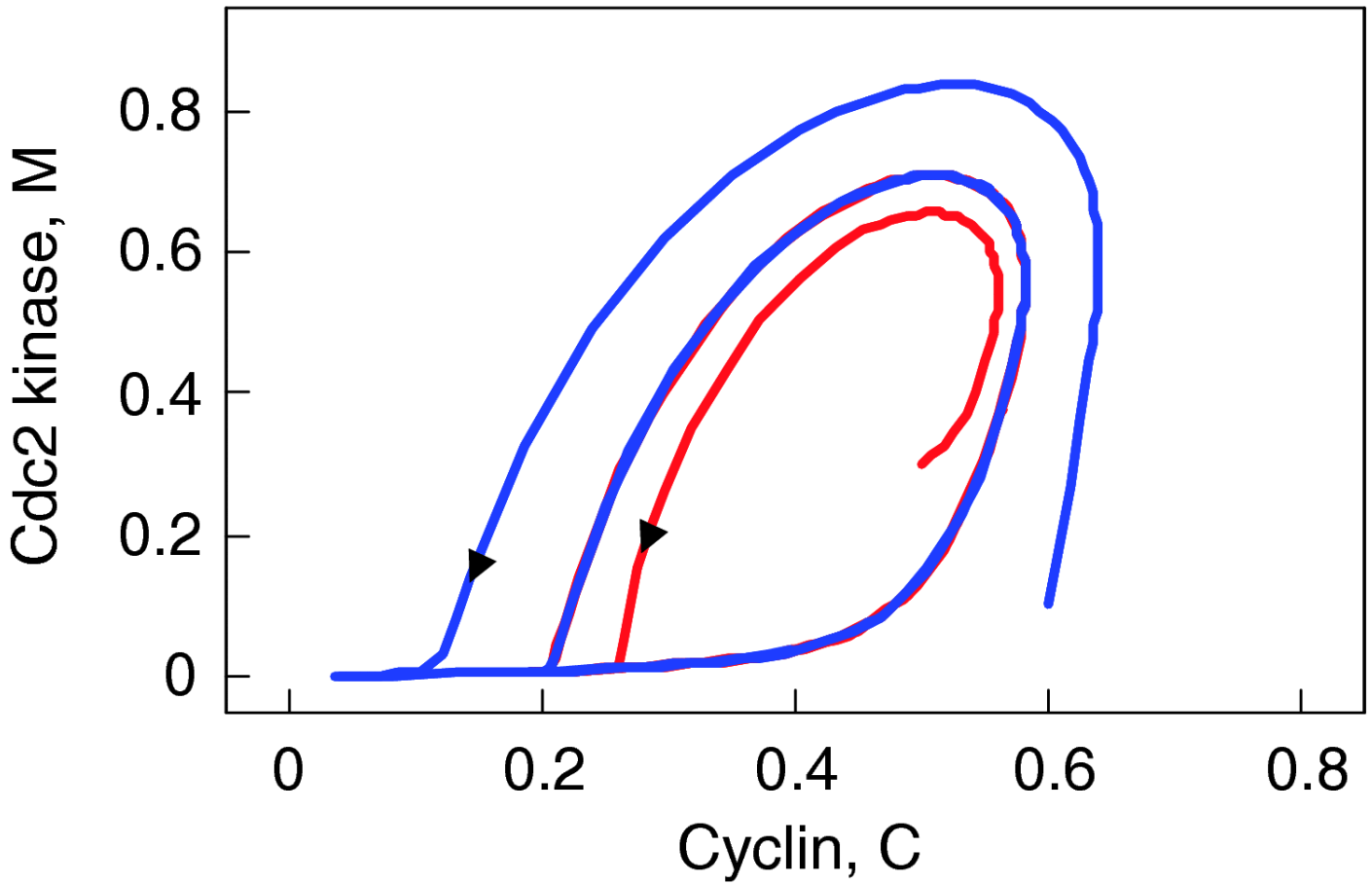
细胞周期模型

Periodicity



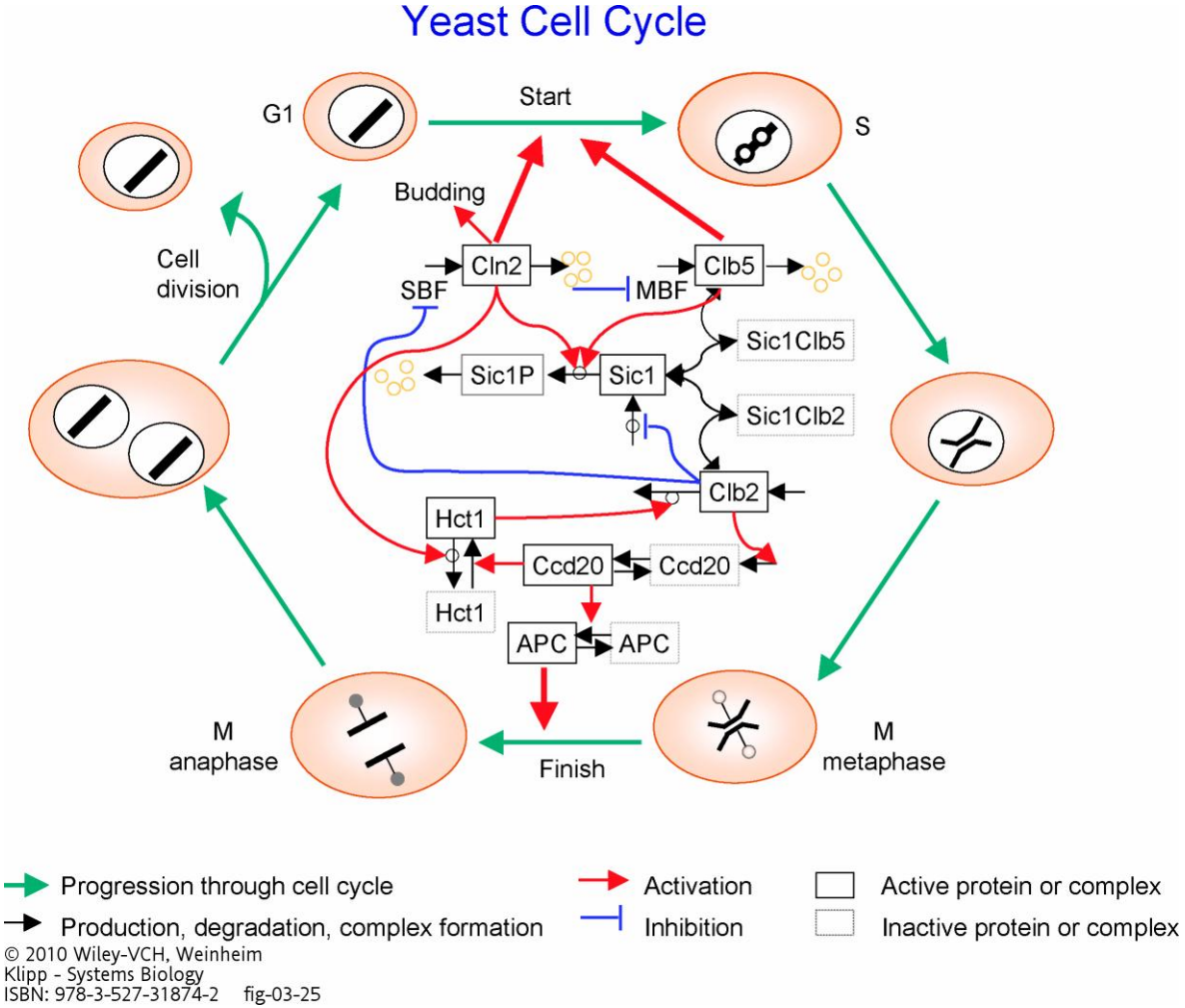
Time courses of cyclin (*C*), active Cdc2 kinase (*M*), and active cyclin protease (*X*) exhibiting oscillations. Initial conditions are $X(0) = 0.01$. Units: μM and min−1.

细胞周期模型



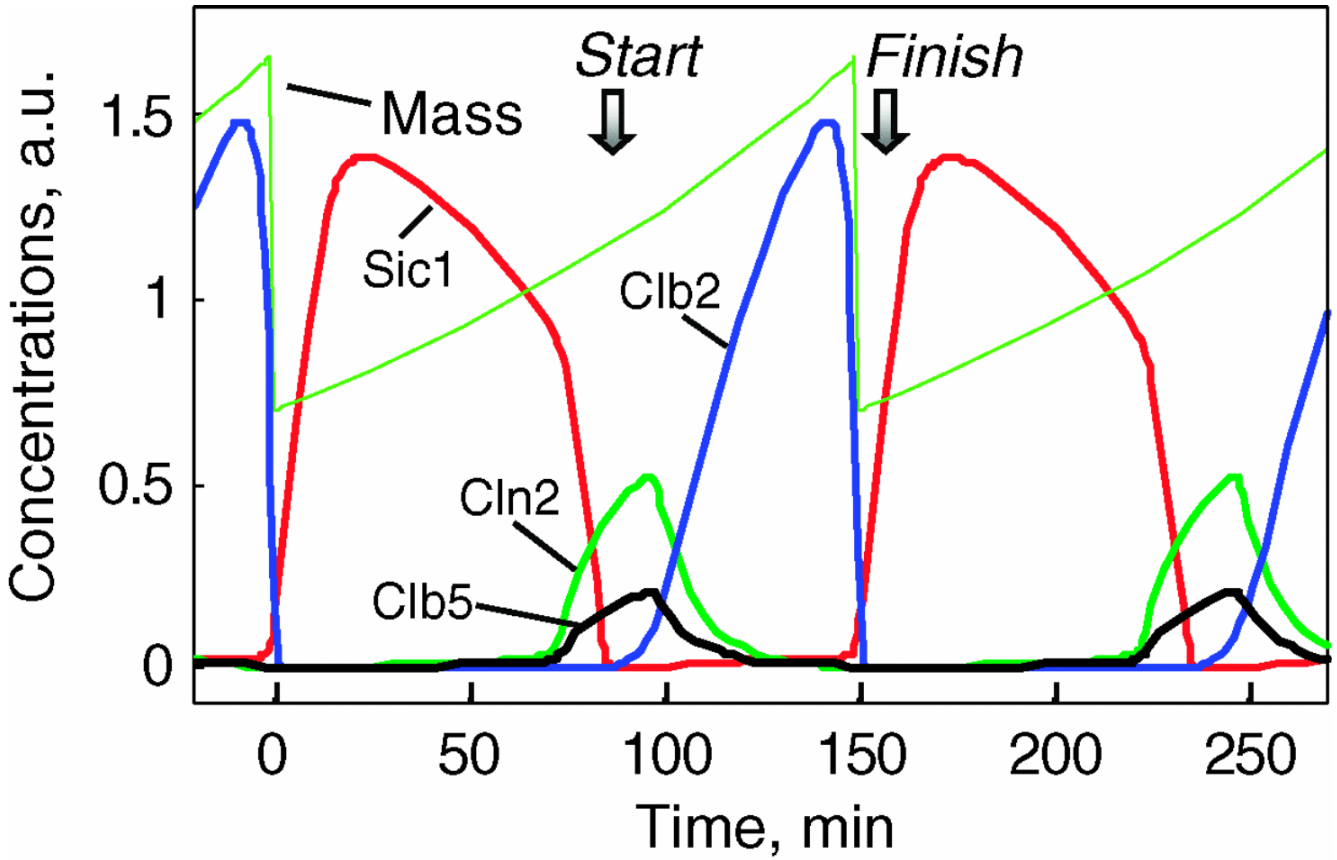
Limit cycle behavior, represented for the variables *C* and *M*.

细胞周期模型



More complicated model

细胞周期模型



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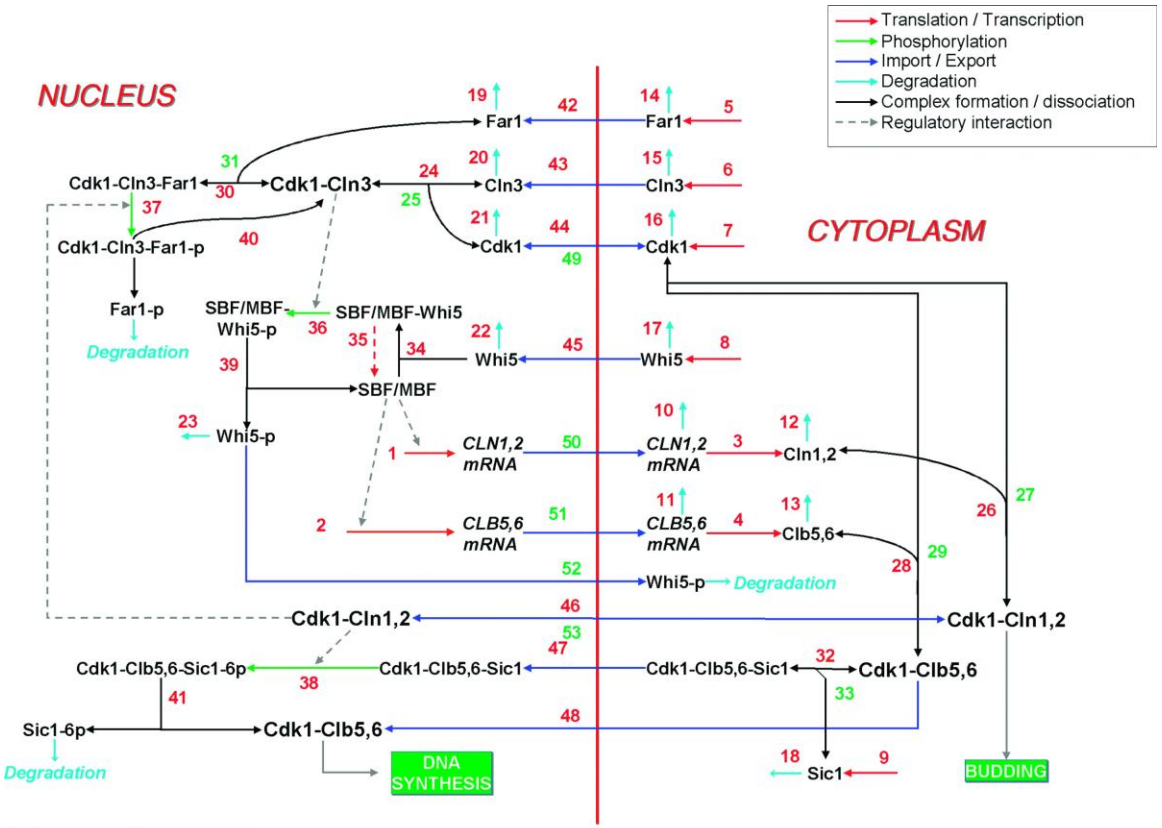
ISBN: 978-3-527-31874-2 fig-03-26

Chen K.C. *et al*. (2000) Molecular Biology of the Cell, 11. 369-391.

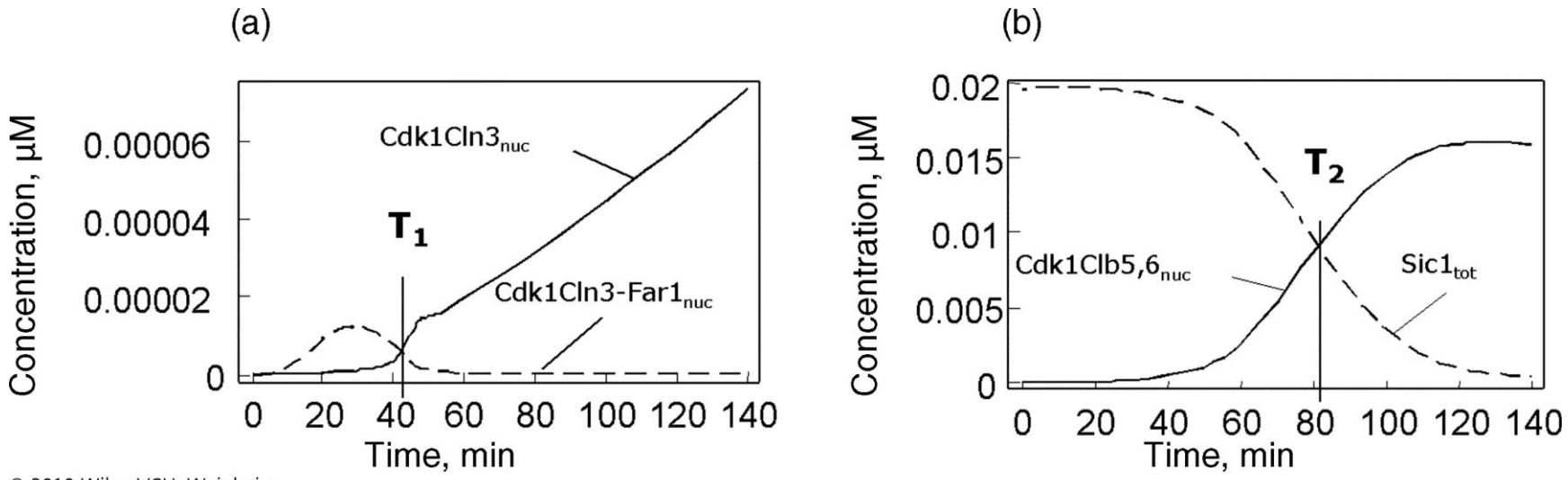
细胞周期模型

Modeling of Nucleo/Cytoplasmatic Compartmentalization



Barberis M, *et al*. (2007) PLoS Comput. Biol. **3**, e64

细胞周期模型



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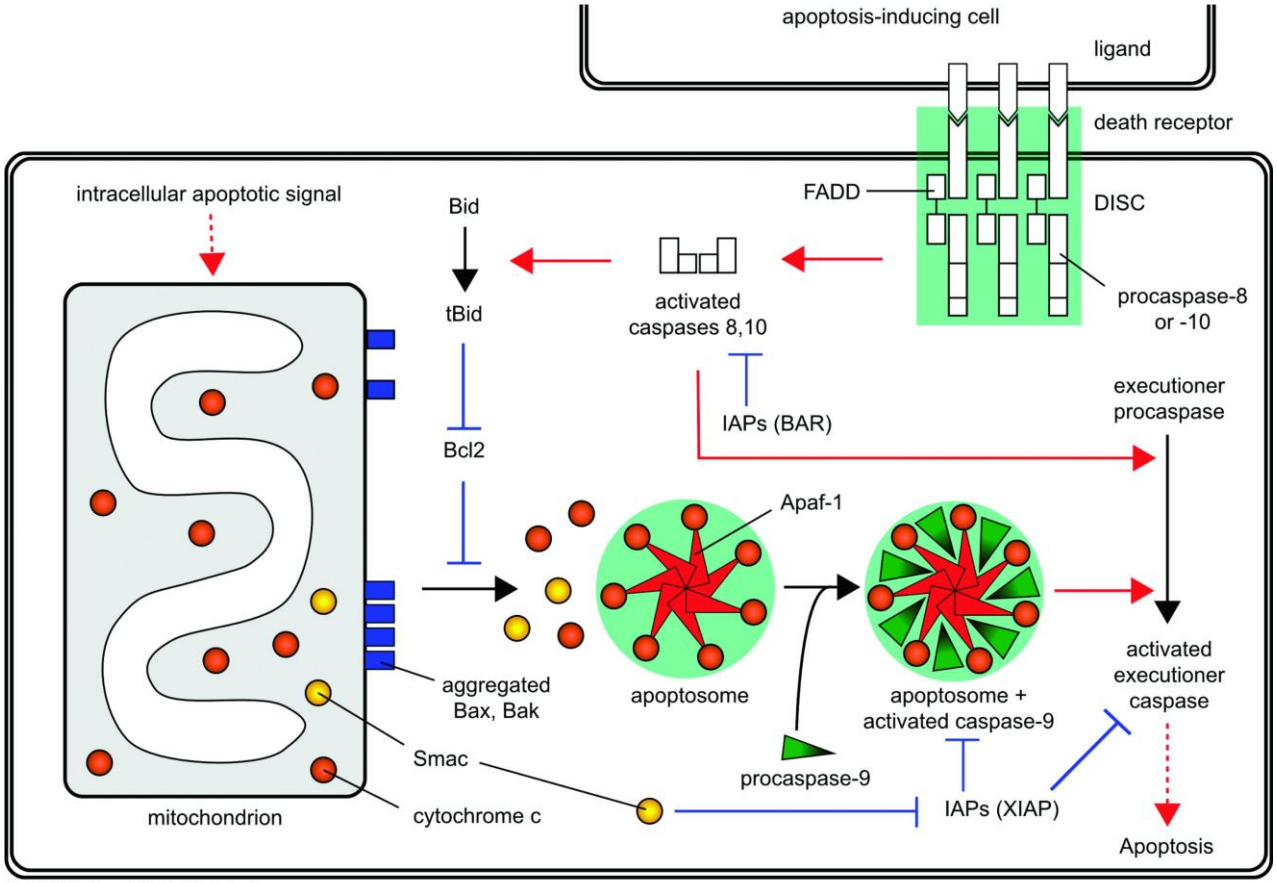
Barberis M, *et al*. (2007) PLoS Comput. Biol. **3**, e64

细胞凋亡模型

细胞凋亡模式图



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细胞凋亡模型

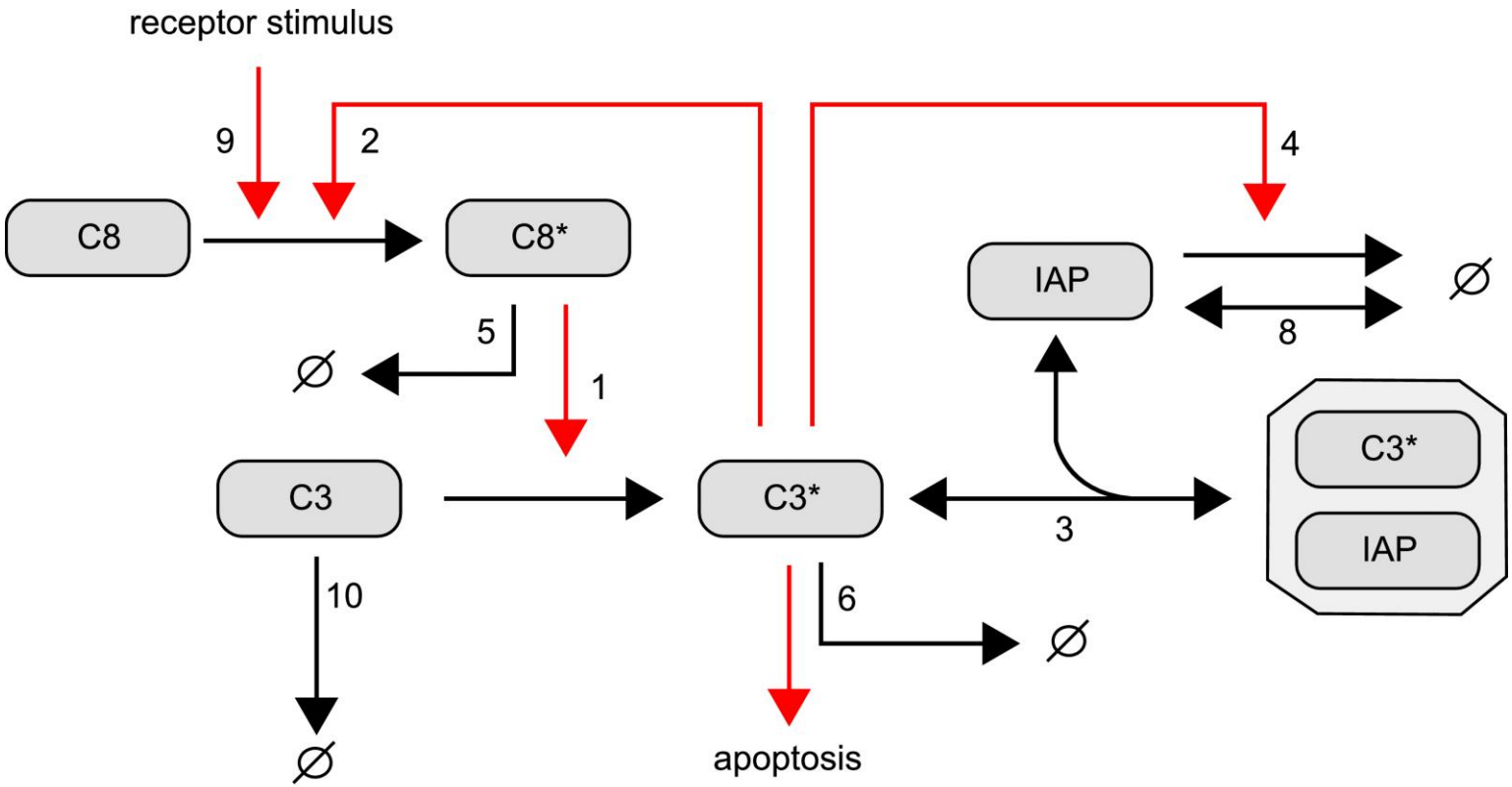
Table 3.5 Predicted effects of combined therapies based on simultaneous extrinsic- and intrinsic-induced apoptosis[a].

	Overexpression				Disruption or mutation	
	Bcl-2/Bcl-X_L	Bax/Bad/Bik	FLIPs	IAPs	FADD	P53
Bcl-2/Bcl-X_L	−	−	+	+	+	−
Bax/Bad/Bik	−	−	−	+	−	−
FLIPs	+	−	−	+	−	+
IAPs	+	+	+	+	+	+
FADD	+	−	−	+	−	+
P53	−	−	−	+	+	−

[a]Entries in the diagonal denote therapies with a single target; others are combinations of potential therapies. A plus sign (+) denotes therapies with decreased activation of executioner caspase, and the minus sign (−) denotes the opposite [65].

细胞凋亡模型

Modeling of Apoptosis



Outline of the apoptotic model developed by Eissing *et al.* (JBC 279: 36892-36897). It comprises the components of the extrinsic pathway of apoptosis. The asterisk denotes the activated form of a caspase.

细胞凋亡模型

动力学方程

$$
\begin{cases}
\dfrac{d[C8]}{dt} = -v_2 - v_9 \\
\dfrac{d[C8^*]}{dt} = v_2 - v_5 \\
\dfrac{d[C3]}{dt} = -v_1 - v_{10} \\
\dfrac{d[C3^*]}{dt} = v_1 - v_3 - v_6 \\
\dfrac{d[IAP]}{dt} = -v_3 - v_4 - v_8 \\
\dfrac{d[C3^* \sim IAP]}{dt} = -v_2 - v_9 \\
\dfrac{d[BAR]}{dt} = -v_{11} - v_{13} \\
\dfrac{d[C8^* \sim BAR]}{dt} = -v_{11} - v_{13}
\end{cases}
$$

速率方程

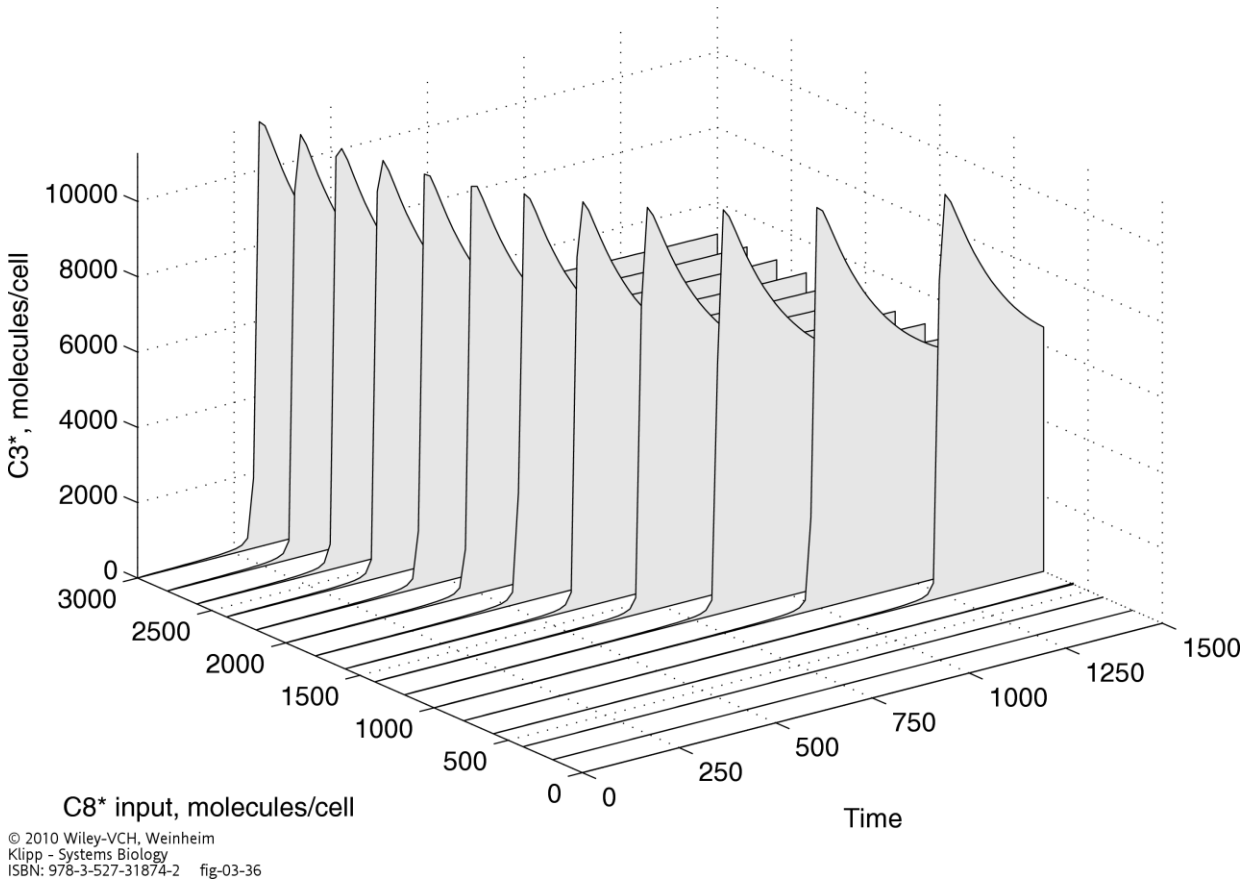
$$
\begin{cases}
v_1 = k_1 \cdot [C8^*] \cdot [C3] \\
v_2 = k_2 \cdot [C3^*] \cdot [C8] \\
v_3 = k_3 \cdot [C3^*] \cdot [IAP] - k_{-3} \cdot [C3^* \sim IAP] \\
v_4 = k_4 \cdot [C3^*] \cdot [IAP] \\
v_5 = k_5 \cdot [C8^*] \\
v_6 = k_6 \cdot [C3^*] \\
v_7 = k_7 \cdot [C3^* \sim IAP] \\
v_8 = k_8 \cdot [IAP] - k_{-8} \\
v_9 = k_9 \cdot [C8] - k_{-9} \\
v_{10} = k_{10} \cdot [C3] - k_{-10} \\
v_{11} = k_{11} \cdot [C8^*] \cdot [BAR] - k_{-11} \cdot [C8^* \sim BAR] \\
v_{12} = k_{12} \cdot [BAR] - k_{-12} \\
v_{13} = k_{13} \cdot [C8^* \sim BAR]
\end{cases}
$$

细胞凋亡模型

Table 3.6 Parameter values of the model described by Eissing *et al.* [66].

Parameter	Value	Reverse parameter	Value
k_1	5.8×10^{-5} cell min^{-1} mo^{-1}	K_{-1}	0
k_2	10^{-5} cell min^{-1} mo^{-1}	k_{-2}	0
k_3	5×10^{-4} cell min^{-1} mo^{-1}	k_{-3}	0.21 min^{-1}
k_4	3×10^{-4} cell min^{-1} mo^{-1}	k_{-4}	0
k_5	5.8×10^{-3} min^{-1}	k_{-5}	0
k_6	5.8×10^{-3} min^{-1}	k_{-6}	0
k_7	1.73×10^{-2} min^{-1}	K_{-7}	0
k_8	1.16×10^{-2} min^{-1}	k_{-8}	464 mo $cell^{-1}$ min^{-1}
k_9	3.9×10^{-3} min^{-1}	k_{-9}	507 mo $cell^{-1}$ min^{-1}
k_{10}	3.9×10^{-3} min^{-1}	k_{-10}	81.9 mo $cell^{-1}$ min^{-1}
k_{11}	5×10^{-4} min^{-1}	k_{-11}	0.21 min^{-1}
k_{12}	10^{-3} min^{-1}	k_{-12}	40 mo $cell^{-1}$ min^{-1}
k_{13}	1.16×10^{-2} min^{-1}	k_{-13}	0

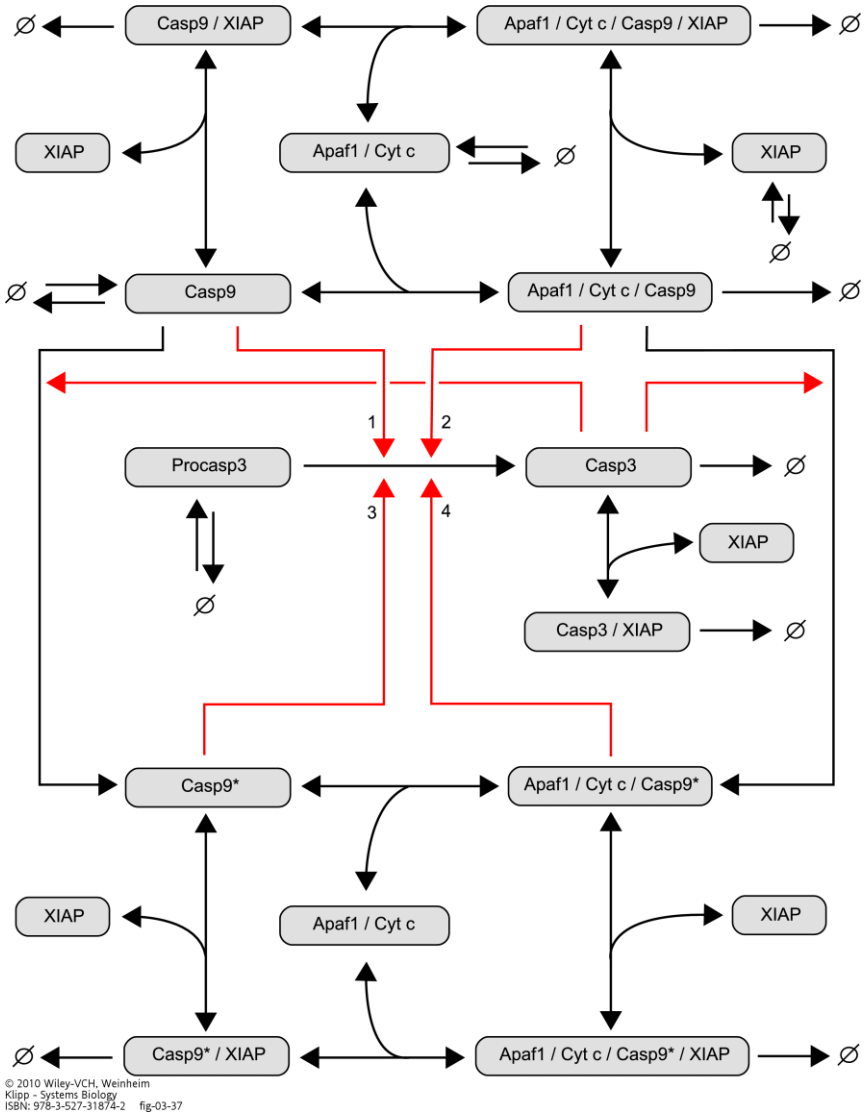
细胞凋亡模型



Bistable behavior of the extrinsic apoptosis model versus varying input signals. The input signal is modeled by the initial concentration of the activated caspase-8 .

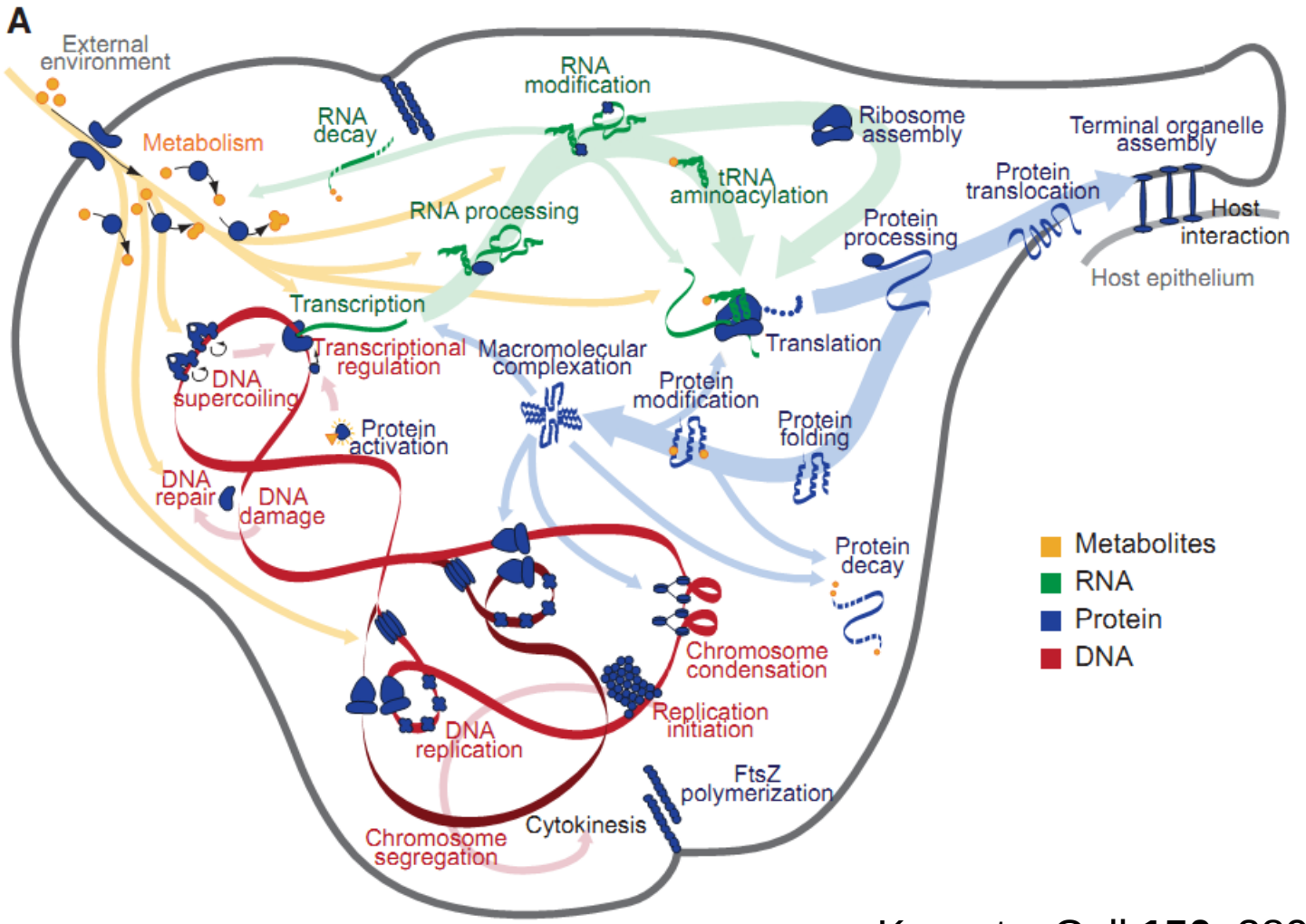
细胞凋亡模型

Intrinsic apoptosis signaling pathway (central part)



Legewie S. *et al*. (2006), PLoS Comput. Biol. **2**, e120.

全细胞计算模型



Karr etc. Cell **150**: 389–401 (2012)