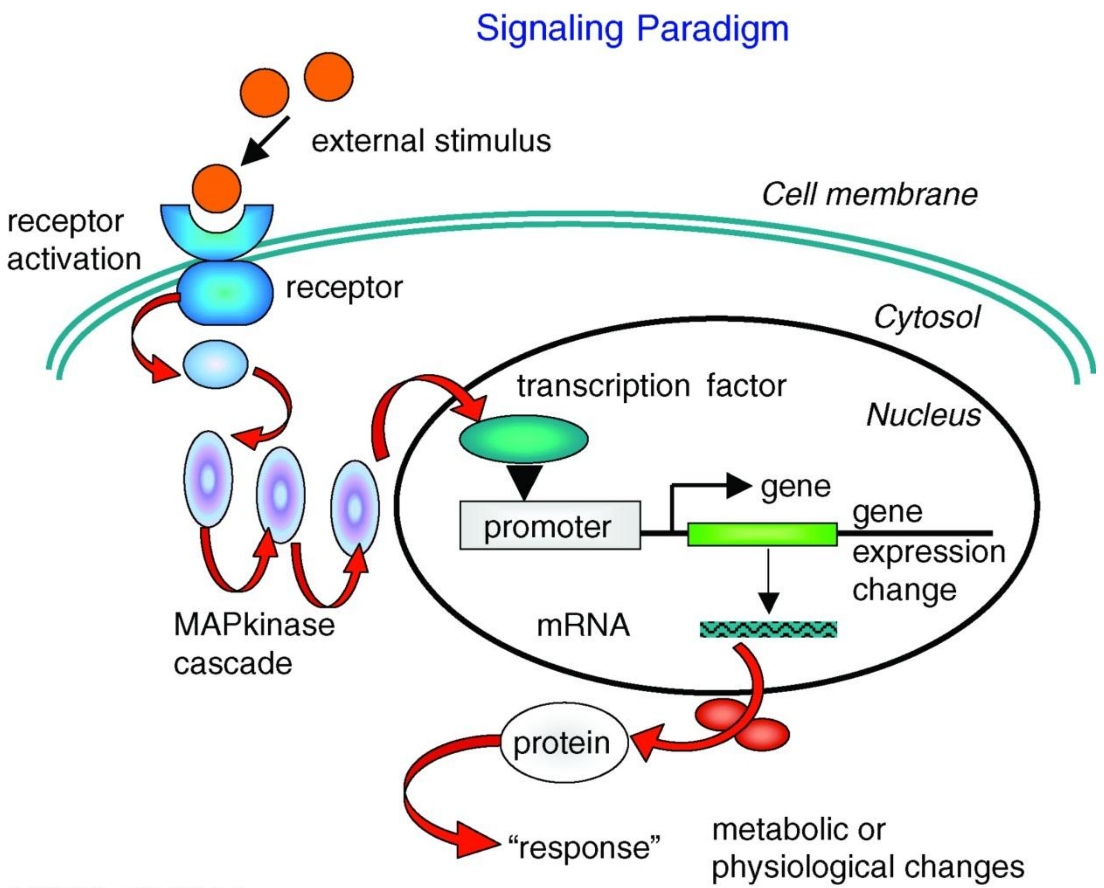
系统生物学
(Systems Biology)

马彬广

信号通路建模

（第十一讲）

信号通路的工作模式



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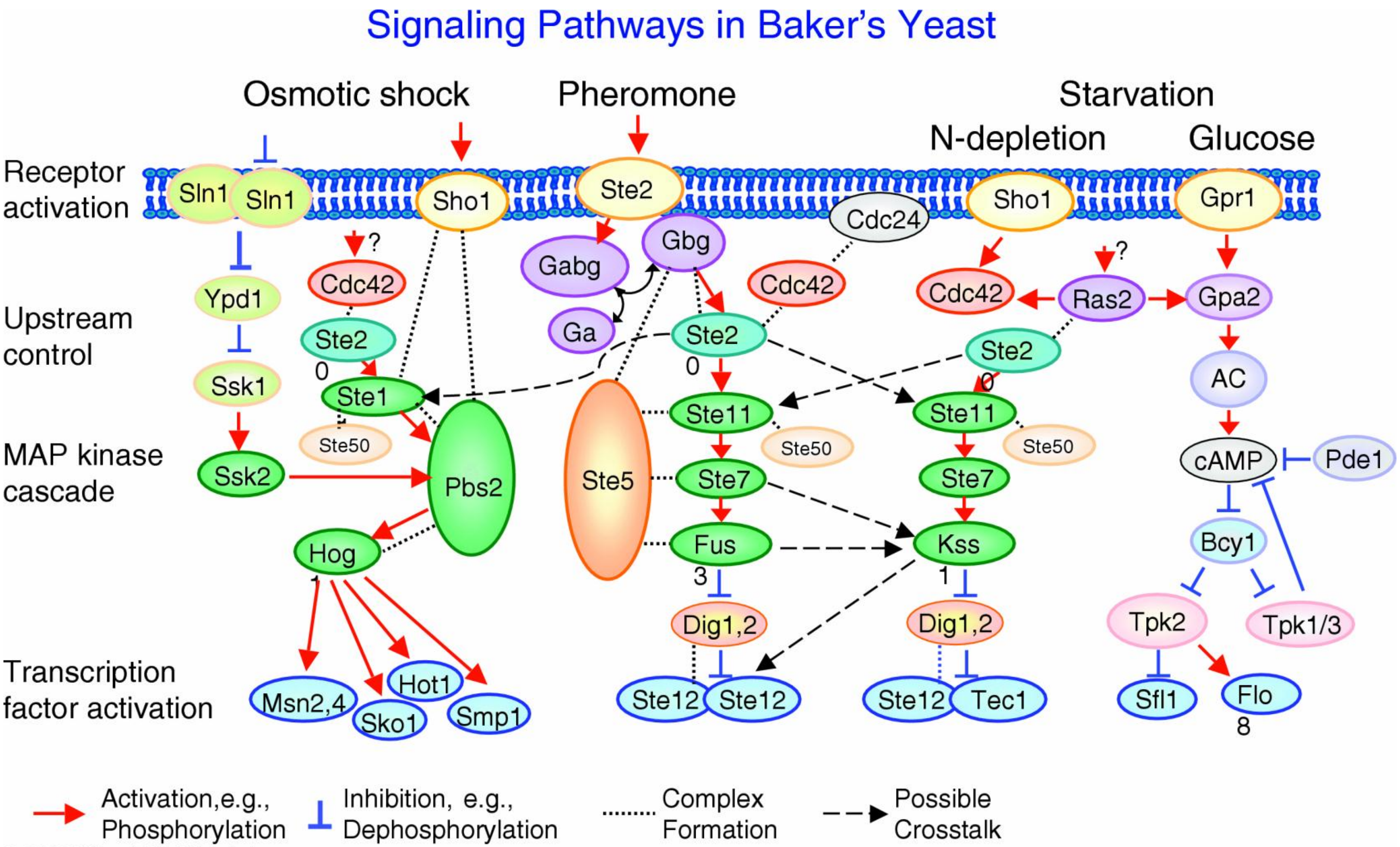
信号通路的工作模式



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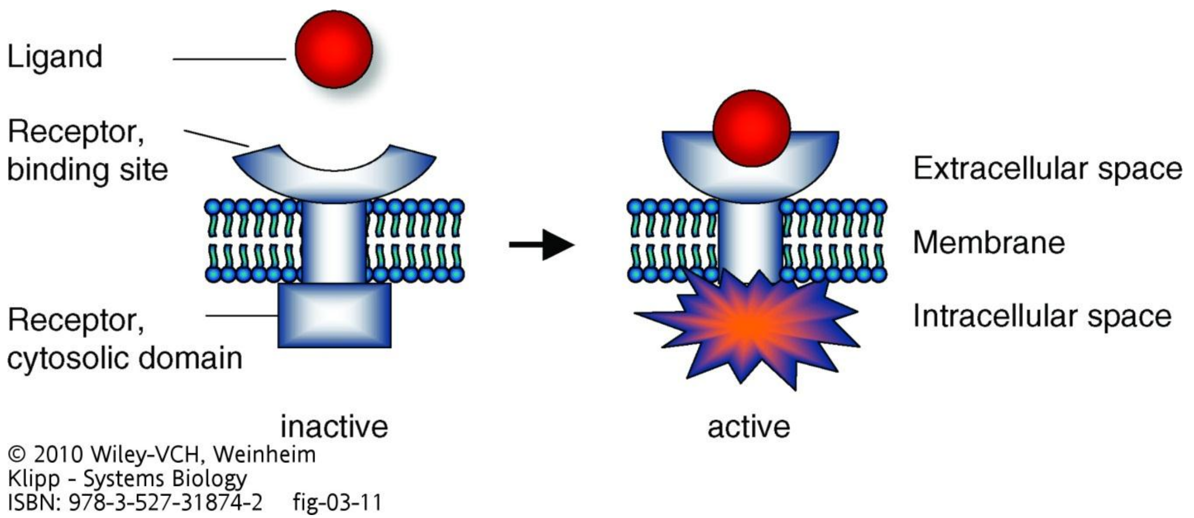
Receptor-Ligand Interactions



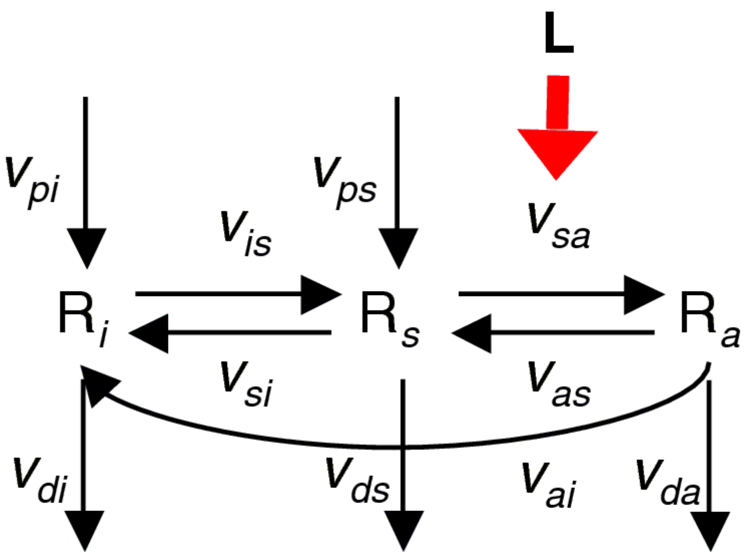
Reversible binding of R and L: $L + R \leftrightarrow LR$

Dissociation constant: $K_D = \dfrac{L \cdot R}{LR} \quad (10^{-12} \sim 10^{-6} M)$

细胞对受体调节

细胞需要有对信号接收器的调节能力，例如降低信号传导的强度以适应长期的刺激。

- 对数量调节：通过生成和降解之间的平衡机制进行调节。
- 对活性调节：由蛋白激酶对丝氨酸、苏氨酸或酪氨酸进行磷酸化来调节。



$$\frac{d}{dt}R_{\mathrm{i}} = v_{\mathrm{pi}} - v_{\mathrm{di}} - v_{\mathrm{is}} + v_{\mathrm{si}} + v_{\mathrm{ai}}$$

$$\frac{d}{dt}R_{\mathrm{s}} = v_{\mathrm{ps}} - v_{\mathrm{ds}} + v_{\mathrm{is}} - v_{\mathrm{si}} - v_{\mathrm{sa}} + v_{\mathrm{as}}$$

$$\frac{d}{dt}R_{\mathrm{a}} = -v_{\mathrm{da}} + v_{\mathrm{sa}} - v_{\mathrm{as}} - v_{\mathrm{ai}}$$

通常：

$v_{\mathrm{p}*} = \mathrm{constant}$ (depend on cell cycle)

$v_{\mathrm{d}*} = k_{\mathrm{d}*} \cdot R_*$; $v_{is} = k_{is} \cdot R_i$

$v_{sa} = k_{sa} \cdot R_s \cdot L$; $v_{sa} = k_{sa} \cdot R_s \cdot \frac{K_B^n \cdot L^n}{1 + K_B^n \cdot L^n}$

K_B: binding constant; n: Hill coefficient.

L – ligand, Ri – inactive receptor, Rs – susceptible receptor, Ra – active receptor.

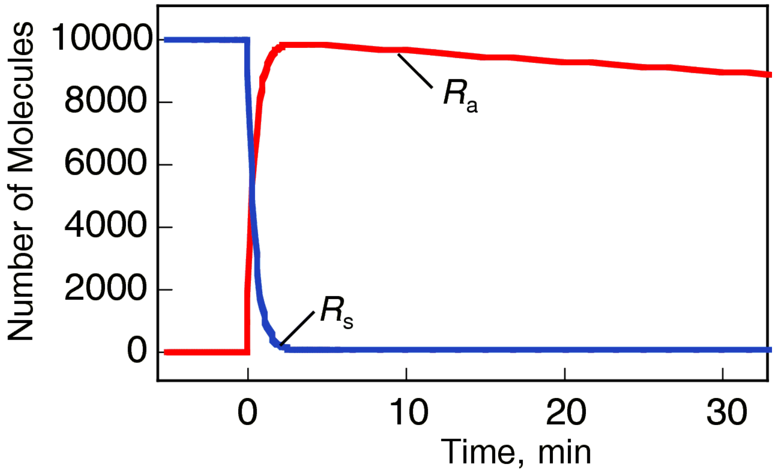
细胞对受体调节

例如，实验确认，在酵母中，由a因子绑定到受体Ste2，而激活的信息素途径，可以做如下建模（Yi etc., PNAS, 100: 10764-10769），只考虑受体的易感和激活状态，(即Ri=0, $v_{*i}=v_{i*}=0$)，而其它速率满足下面的关系：

$$v_{ps} = k_{ps}$$
$$v_{ds} = k_{ds} \cdot R_s$$
$$v_{da} = k_{da} \cdot R_a$$
$$v_{sa} = k_{sa} \cdot R_s \cdot L$$
$$v_{as} = k_{as} \cdot R_a$$

其中，

$$k_{ps} = 4 \text{ molecules per cell per second}$$
$$k_{ds} = 4\times10^{-4} s^{-1}$$
$$k_{da} = 4\times10^{-3} s^{-1}$$
$$k_{sa} = 2\times10^{6} M^{-1} S^{-1}$$
$$k_{as} = 1\times10^{-2} s^{-1}$$



常见的几种信号途径

- G Proteins Pathway
- Small G proteins Pathway
- Phosphorelay Systems
- MAP Kinase Cascades
- Jak/Stat Pathway

G蛋白通路

- G蛋白：trimeric GTP-binding regulatory protein, 3 subunits Gα, Gβ, Gγ, 位于质膜内侧（胞浆一侧），称为switch protein。

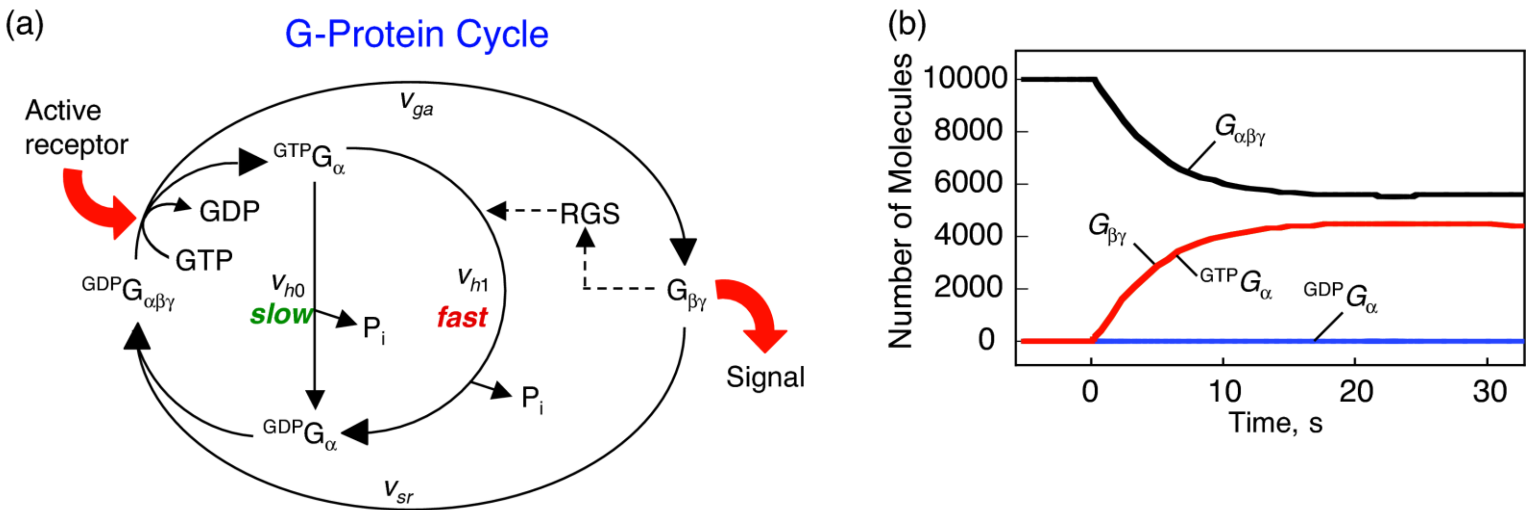
- GPCR: G-protein coupled receptor, a heptahelical transmembrane structure，接受来自外界的刺激，如光，气味，各种激素，神经递质，浓度梯度等。

- Intracelluar effectors: such as adenylyl cyclase，phospholipase C等，产生第二信使, such as cAMP, cGMP.

- G蛋白与GDP绑定，处于失活状态，与GTP绑定，则进入激活状态，GEF促使GDP释放GTP绑定，从而激活G蛋白；GTP水解，形成GDP和Pi，开关蛋白又回到失活的关闭状态。

- GTP水解的速率被GTPase促进蛋白(GAP)和G蛋白信号调节子（RGS）所促进，而被鸟苷酸解离抑制物GDI所抑制。

G蛋白通路



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信号强度受控于：

1、核苷酸交换的速率；
2、GTP自发水解的速率；
3、RGS促进的GTP水解速率；
4、亚基重新组合的速率。

$$\begin{cases} v_{ga} = k_{ga} \cdot R_a \cdot G_{\alpha\beta\gamma} \\ v_{hi} = k_{hi} \cdot G_a GTP, \quad i = 0,1 \\ v_{sr} = k_{sr} \cdot G_{\beta\gamma} \cdot G_\alpha GDP \end{cases}$$

$$\begin{cases} \frac{d}{dt} G_{\alpha\beta\gamma} = -v_{ga} + v_{sr} \\ \frac{d}{dt} G_\alpha GTP = v_{ga} - v_{h0} - v_{h1} \\ G_{\text{total}\alpha} = G_{\alpha\beta\gamma} + G_a GTP + G_\alpha GDP \\ G_{\text{total}\beta\gamma} = G_{\alpha\beta\gamma} + G_{\beta\gamma} \end{cases}$$

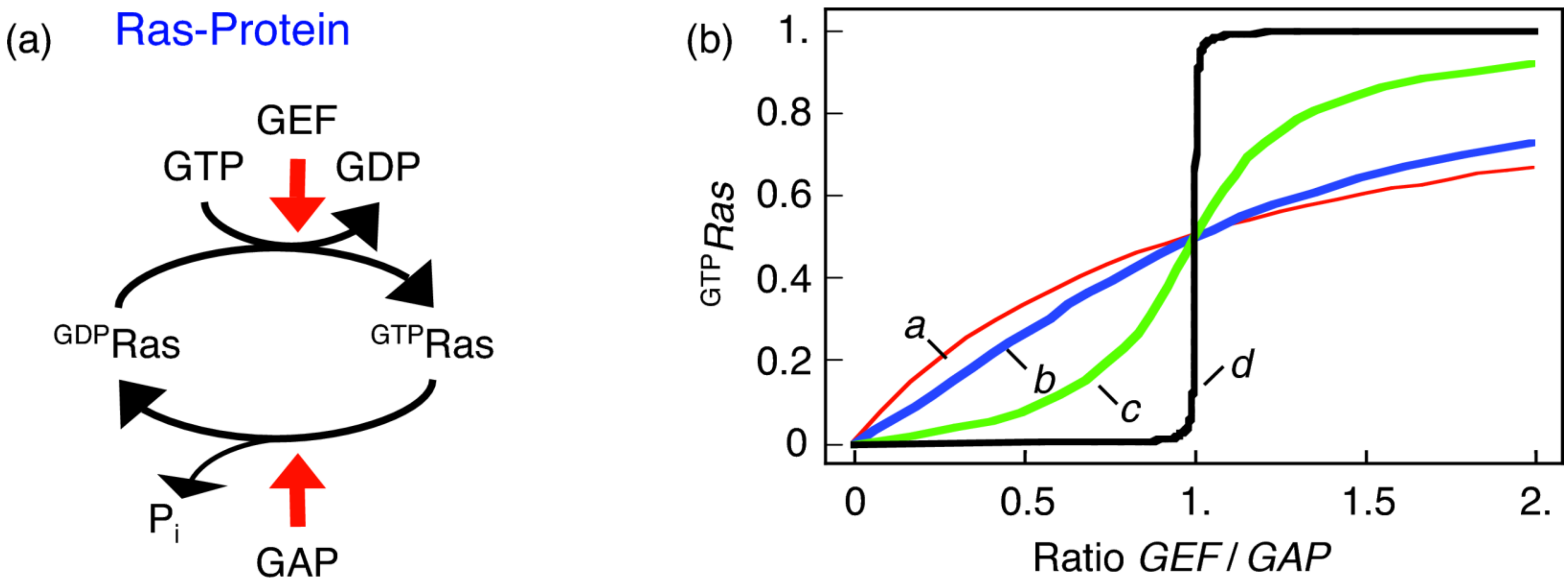
$k_{ga} = 1\times 10^{-5}$ (molecule per cell)$^{-1}$s^{-1}; $k_{h0} = 0.004\ \text{s}^{-1}$;

$k_{h1} = 0.11\ \text{s}^{-1}$; $k_{sr} = 1$ (molecule per cell)$^{-1}$s^{-1}

小G蛋白通路

- Small G protein: monomeric protein with molecular weight of 20-40 kDa.
- Five families: Ras, Rho, Rab, Ran, Arf, usullaly used as timers.
- Activity: depends on GTP-binding, as trimeric G proteins.
- Mutations of Ras protooncogenes (H-Ras, N-Ras, K-Ras) are found in many human tumors. Ras mutants can still bind GAP, but cannot catalyze GTP hydrolysis. Therefore, they stay active for a long time.

小G蛋白通路



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$$\frac{d}{dt}RasGTP = -\frac{d}{dt}RasGDP = v_{\mathrm{GEF}} - v_{\mathrm{GAP}}$$

$$v_{\mathrm{GEF}} = \frac{k_1 \cdot GEF \cdot RasGDP}{K_{\mathrm{m1}} + RasGDP}, \quad v_{\mathrm{GAP}} = \frac{k_2 \cdot GAP \cdot RasGTP}{K_{\mathrm{m2}} + RasGTP}$$

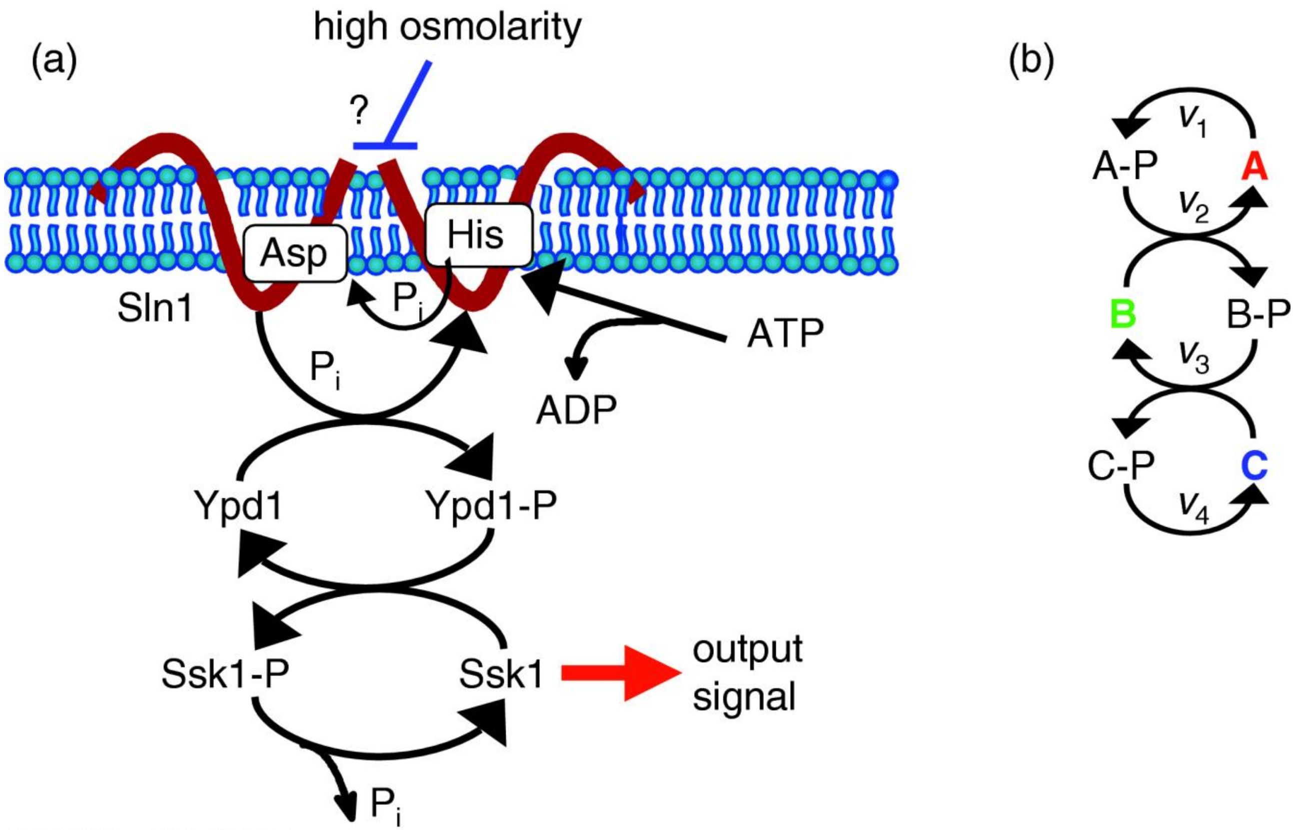
- Most phosphorylation events take place under repeated consumption of ATP.

- Phosphorelay (also called Phosphotransfer) systems employ another mechanism: after an initial phosphorylation using ATP (or other Phosphate donor), the phosphate group is transferred directly from one protein to the next protein without further consumption of ATP. For example, bacterial Phosphoenolpyruvate: carbohydrate phosphotransferase, the two component system of E coli, or Sln1 pathway involved in osmoresponse of yeast.

- See the High Osmolarity Glycerol (HOG) signaling pathway on the next page.

磷酸传递系统

Phosphorelay System

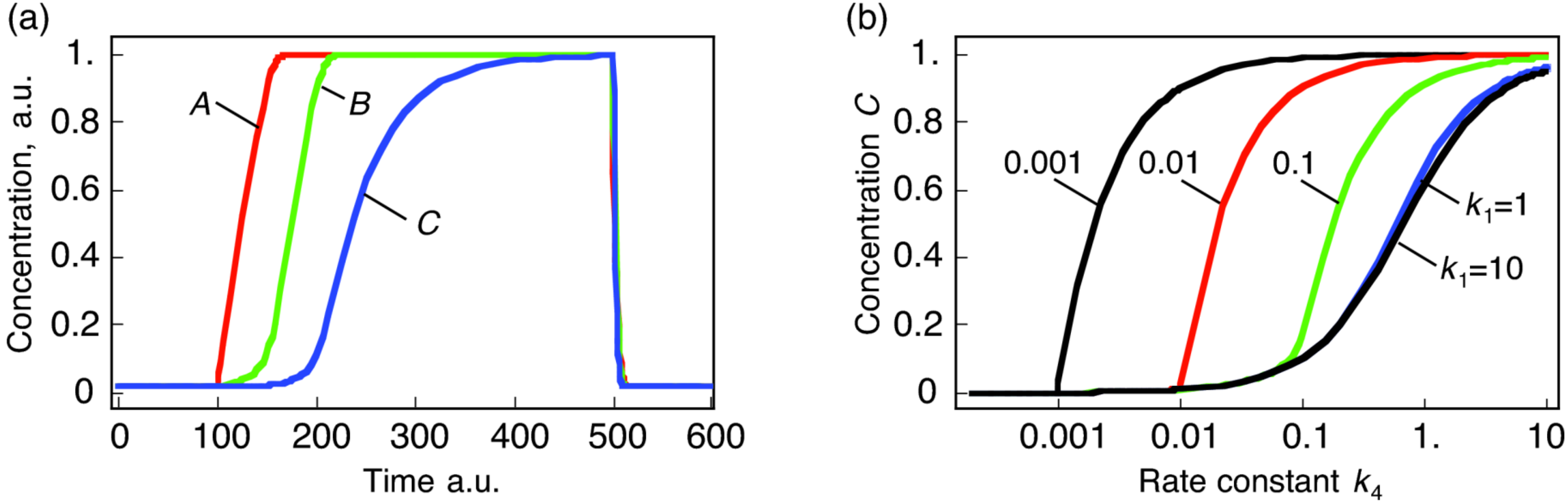


Schematic representation of a phosphorelay system. Phosphorelay system belonging to the Sln1-branch of the HOG pathway in yeast. General scheme of phosphorylation and dephosphorylation in a phosphorelay.

磷酸传递系统

$$\begin{cases} \frac{d}{dt}A = -k_1 \cdot A + k_2 \cdot AP \cdot B \\ \frac{d}{dt}B = -k_2 \cdot AP \cdot B + k_3 \cdot BP \cdot C \\ \frac{d}{dt}C = -k_3 \cdot BP \cdot C + k_4 \cdot CP \end{cases}$$

$$\begin{cases} A_{\text{total}} = A + AP \\ B_{\text{total}} = B + BP \\ C_{\text{total}} = C + CP \end{cases}$$



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Time courses after stimulation from time 100 to time 500 (a.u.) by decreasing $k1$ to zero. Dependence of steady-state level of the phosphorelay output, C, on the cascade activation strength, $k1$, and the terminal dephosphorylation, $k4$. Parameter values: $k1 = k2 = k3 = 1$, $k4 = 0.02$, $A\text{total} = B\text{total} = C\text{total} = 1$.

蛋白激酶级联途径

- Mitogen-activated protein kinases (MAPKs) are a family of serine/threonine kinases that transduce signal from the cell membrane to the nucleus in response to a wide range of stimuli.

- Independent or coupled kinase cascades participate in many different intracellular signaling pathways that control cell growth, differetiation, transformation, and apoptosis.

- MAPK cascades are widely involved in eukaryotic signal transduction and MAP kinase pathways are conserved from yeast to mammals.

- MAPK cascades are multi-level (usually 3 or 4 levels) phosphrylation systems where the activated kinase at each level phosphorylates the kinase at the next level down the cascade.

- See an example on the next page.

蛋白激酶级联途径

MAP Kinase Cascade

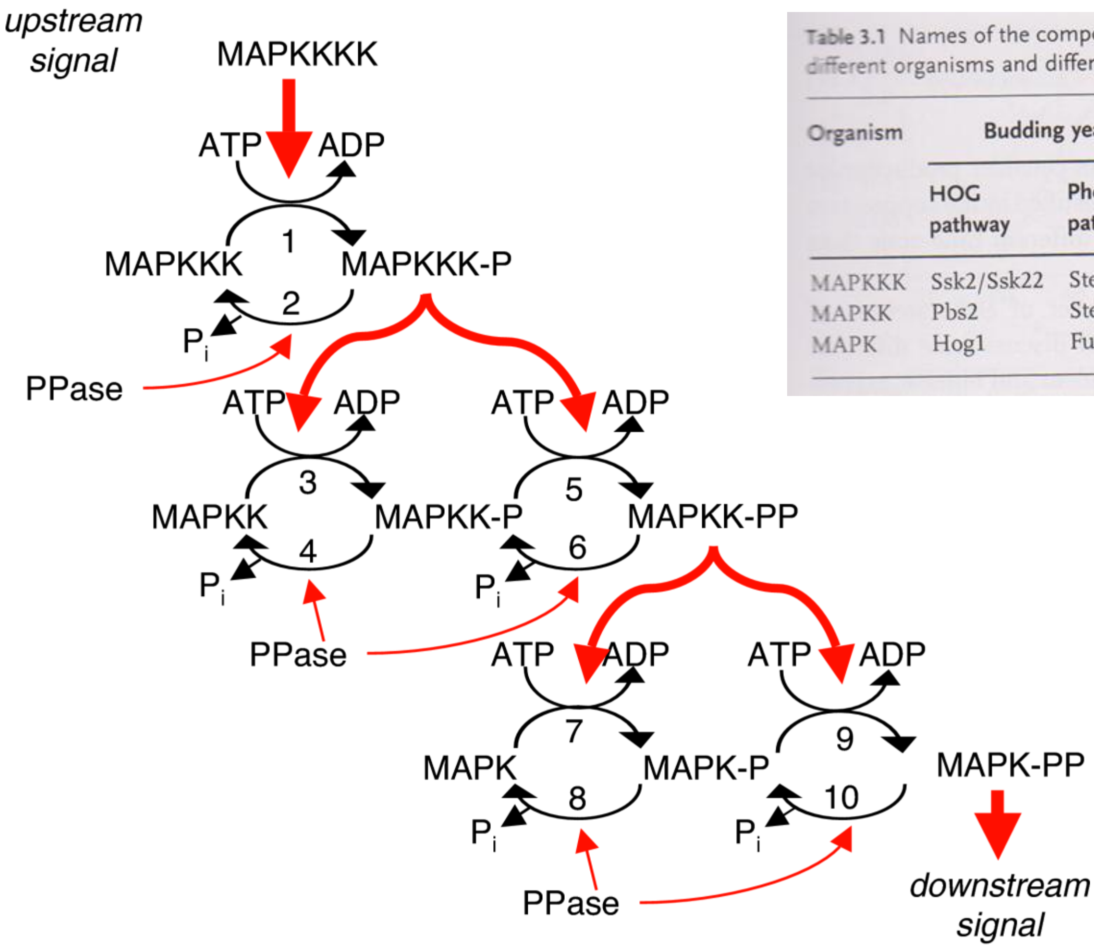

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Table 3.1 Names of the components of MAP kinase pathways in different organisms and different pathways.

Organism	Budding yeast		Xensopus oocytes	Human, cell cycle regulation		
	HOG pathway	Pheromone pathway			p38 pathway	JNK pathway
MAPKKK	Ssk2/Ssk22	Ste11	Mos	Rafs (c-, A- and B-),	Tak1	MEKKs
MAPKK	Pbs2	Ste7	MEK1	MEK1/2	MKK3/6	MKK4/7
MAPK	Hog1	Fus3	p42 MAPK	ERK1/2	p38	JNK1/2

蛋白激酶级联途径

动力学方程

$$
\begin{cases}
\frac{d}{dt}MAPKKK = -v_1 + v_2 \\
\frac{d}{dt}MAPKKK\_P = v_1 - v_2 \\
\frac{d}{dt}MAPKK = -v_3 + v_4 \\
\frac{d}{dt}MAPKK\_P = v_3 - v_4 - v_5 + v_6 \\
\frac{d}{dt}MAPKK\_P_2 = v_5 - v_6 \\
\frac{d}{dt}MAPK = -v_7 + v_8 \\
\frac{d}{dt}MAPK\_P = v_7 - v_8 - v_9 + v_{10} \\
\frac{d}{dt}MAPK\_P_2 = v_9 - v_{10}
\end{cases}
$$

守恒关系

$$
\begin{cases}
MAPKKK_{total} = MAPKKK + MAPKKK\_P \\
MAPKK_{total} = MAPKK + MAPKK\_P + MAPKK\_P_2 \\
MAPK_{total} = MAPK + MAPK\_P + MAPK\_P_2
\end{cases}
$$

速率选择

以第1，2个反应为例，根据简单的质量作用定律：

$$
\begin{cases}
v_1 = k_{kinase} \cdot MAPKKK \cdot MAPKKKK \\
v_2 = k_{phosphatase} \cdot MAPKKK\_P
\end{cases}
$$

蛋白激酶级联途径

如果显式考虑ATP和ADP，则：

$$\begin{cases} v_1 = k_{kinase} \cdot MAPKKK \cdot MAPKKKK \cdot ATP \\ v_2 = k_{phosphatase} \cdot MAPKKK\_P \end{cases}$$

此时考虑ATP和ADP的平衡，需要增加三个方程：

$$\begin{cases} \frac{d}{dt}ATP = -\frac{d}{dt}ADP = -\sum_{i \text{ odd}} v_i \\ \frac{d}{dt}P_i = \sum_{i \text{ even}} v_i \end{cases}$$

此时，还存在两个守恒关系：

$$\begin{cases} ATP + ADP = \text{constant} \\ MAPKKK\_P + MAPKK\_P + 2MAPKK\_P_2 + MAPK\_P + 2MAK\_P_2 + 3ATP + 2ADP + P = \text{constant} \end{cases}$$

蛋白激酶级联途径

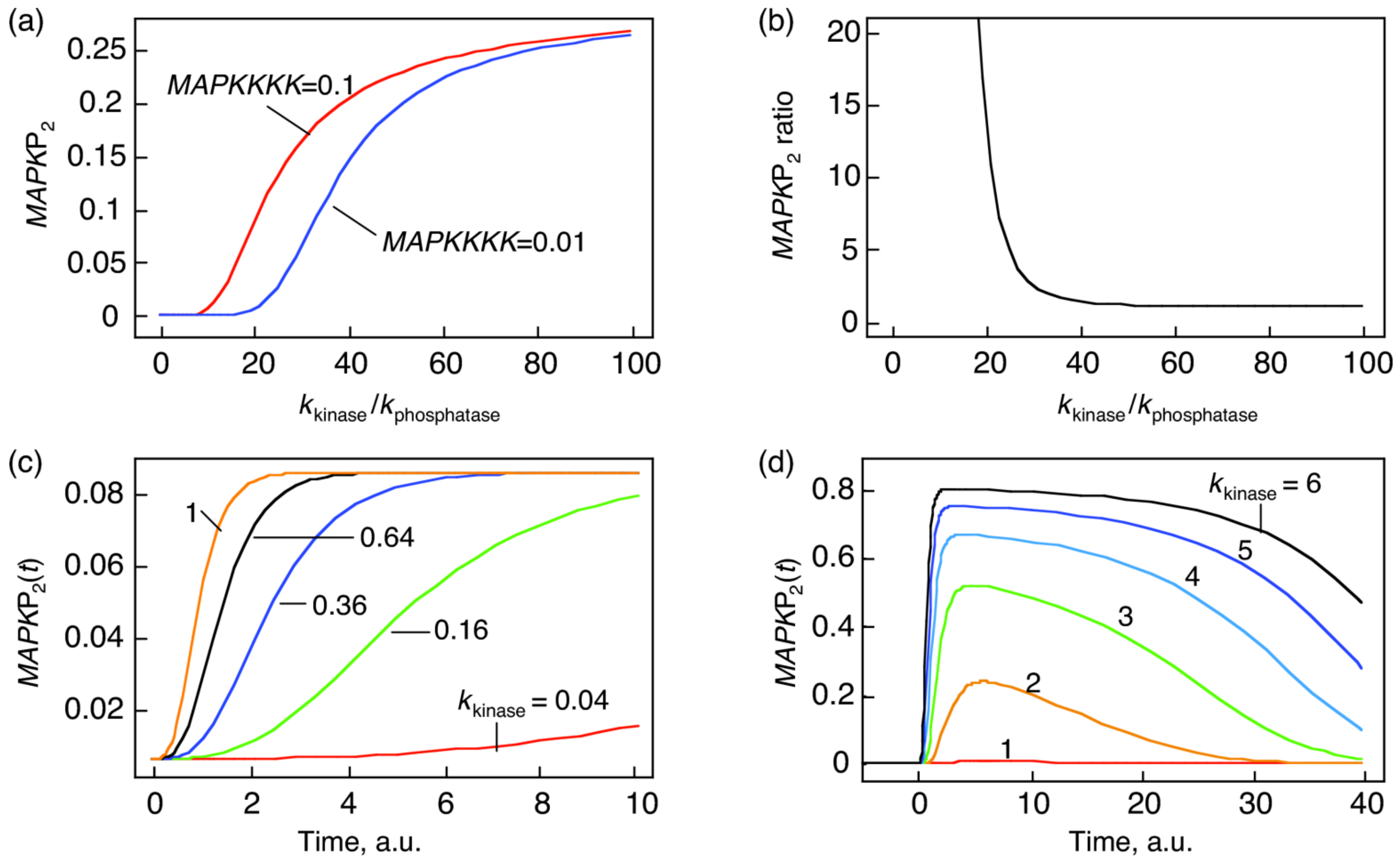
也可以用米氏动力学去表示反应速率：

$$\begin{cases} v_1 = k_1 \cdot MAPKKKK \dfrac{MAPKKK}{K_{m1} + MAPKKK} \\ v_2 = \dfrac{V_{\max 2} \cdot MAPKKK\_P}{K_{m2} + MAPKKK\_P} \end{cases}$$

有文献报道，米氏常数K_{m1}和K_{m2}的取值为：15nM, 46nM和159nM, 300nM, 最大速率V_{max}取值，0.75 nM s^{-1}.

MAPK激酶途径的信号传导能力，可由级联末端MAPKP2的浓度来表征，依赖于动力学常数k_{kinase}和$k_{phosphatase}$，以及它们的比值，$k_{kinase}/k_{phosphatase}$，详细分析如后图所示。

蛋白激酶级联途径



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$k_{kinase}/k_{phosphatase} = 20$

$k_{phosphatase} = 1$

Jak/Stat Pathways

- Jak/Stat pathways important for regulating immune responses and cellular homeostasis.

- Activated by cytokines, a large family of extracellular ligands.

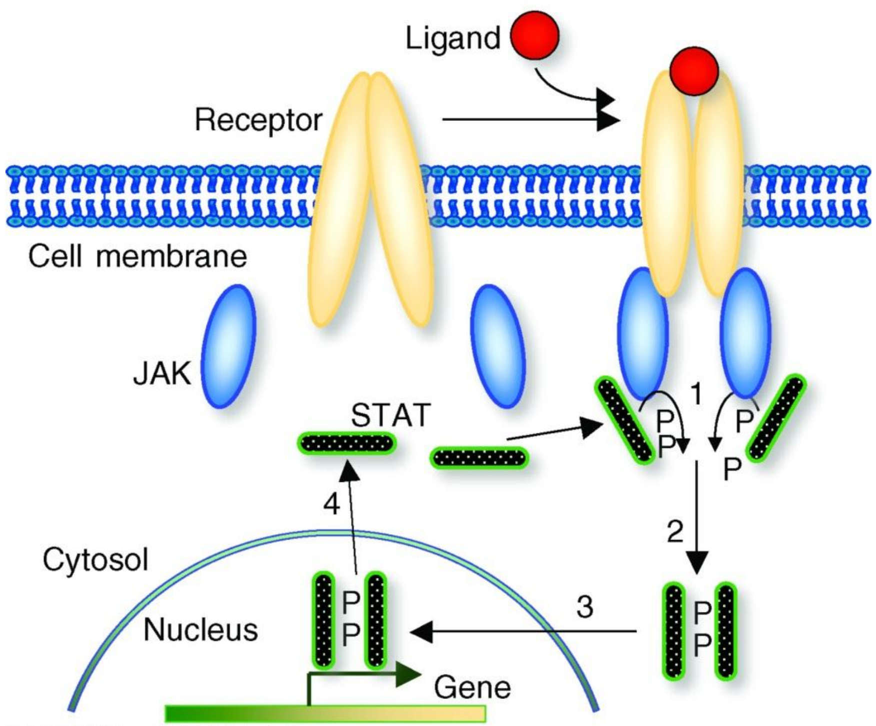
- The whole family of conserved receptors comprises 4 Jaks and 7 Stats.

- Downstream signaling entails tyrosine phosphorylation.

- Stat stands for “signal transducer and transcription activator”.

- Inactive as monomer and activation involves phosphorylation and dimerization.

Jak/Stat Pathways



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$$\begin{cases} \dfrac{dx_1(t)}{dt} = -k_1 \cdot x_1(t) \cdot EpoR_A + 2k_4 \cdot x_3(t-\tau) \\ \dfrac{dx_2(t)}{dt} = -k_2 \cdot x_2^2(t) + k_1 \cdot x_1(t) \cdot EpoR_A \\ \dfrac{dx_3(t)}{dt} = -k_3 \cdot x_3(t) + k_2 \cdot x_2^2(t) \\ \dfrac{dx_4(t)}{dt} = -k_4 \cdot x_3(t-\tau) + k_3 \cdot x_3(t) \end{cases}$$

其中，$x_1 =$ monomeric $Stat5$, $x_2 = Stat5\_P$,
$x_3 =$ dimeric $Stat5$ in cytosol,
$x_4 =$ dimeric $Stat5$ in nucleus.

Swamaye etc. (2003)

信号通路属性的定量指标

设用P_i（t）表示激酶i（或其它感兴趣的物质）依赖于时间的浓度，则有下列指标：

信号期间物质i的总生成量： $I_i = \int_0^\infty P_i(t)dt$

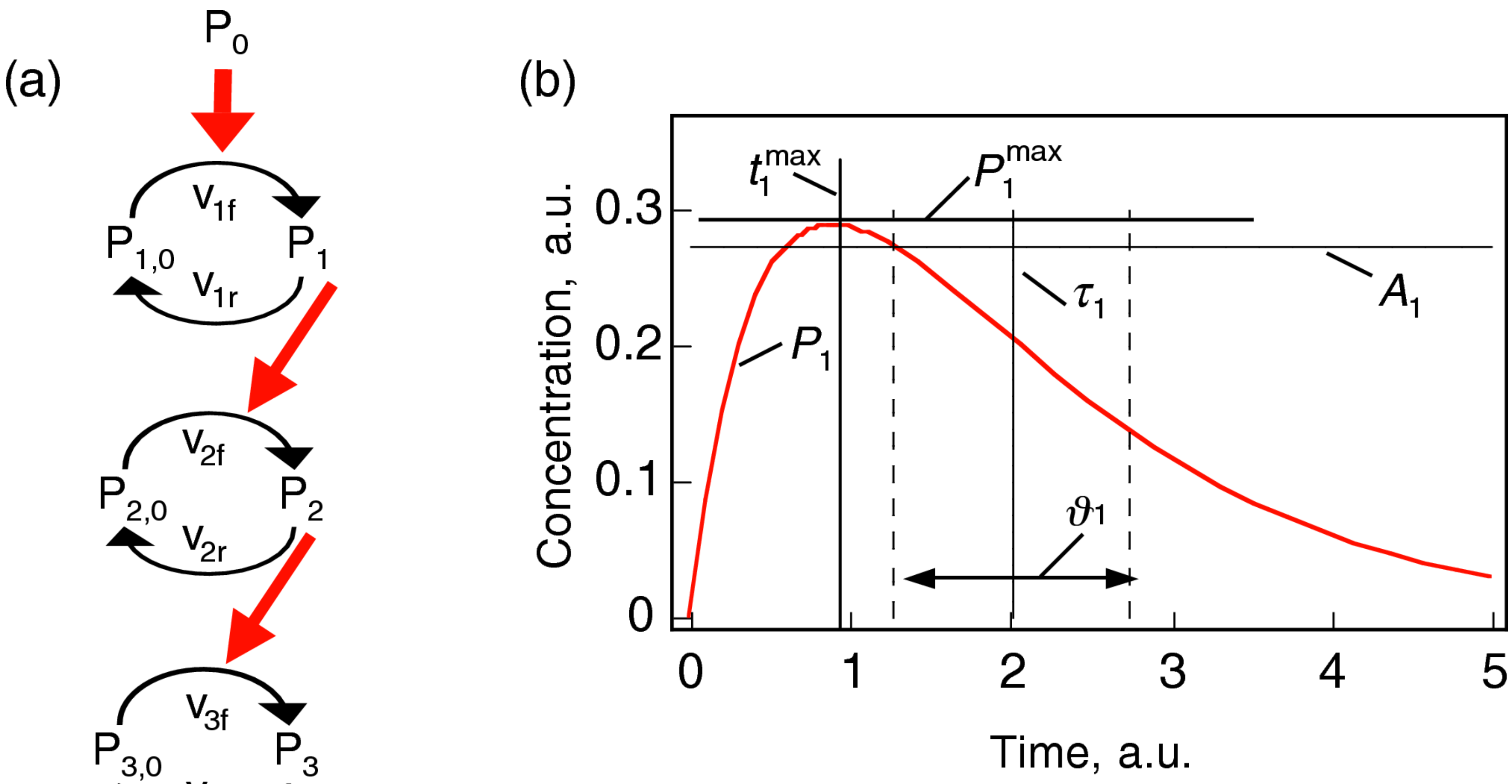
时间加权量： $T_i = \int_0^\infty t \cdot P_i(t)dt$ 和 $Q_i = \int_0^\infty t^2 \cdot P_i(t)dt$

信号时刻： $\tau_i = \dfrac{T_i}{I_i}$ 信号时长（duration）： $\vartheta_i = \sqrt{Q_i / I_i - \tau_i^2}$

信号强度（amplitude）： $A_i = \dfrac{I_i}{2\vartheta_i}$

A_i的几何意义，是某矩形的高，未必等于P_i的最大值。

信号通路属性的定量指标



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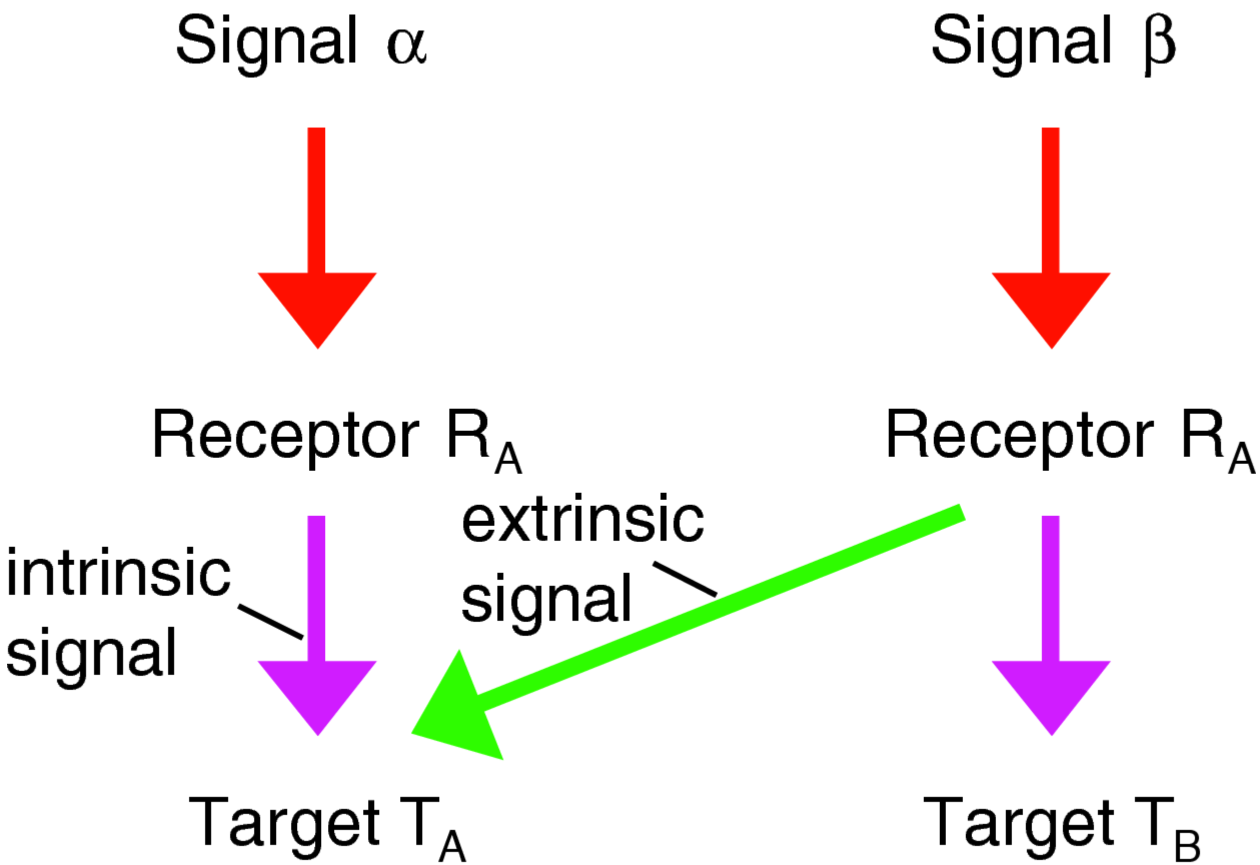
Wiring of an example signaling cascade with $v_{if} = k_{if} \cdot P_{i-1}(t) \cdot (1 - P_i(t))$, $v_{ir} = k_{ir} \cdot P_i(t)$, $k_{if} = k_{ir} = 1$, $dP_0(t)/dt = -P_0(t)$, $P_0(0) = 1$, $P_i(0) = 0$ for $i = 1, \ldots, 3$. Time course of P_1.

信号通路属性的定量指标

Table 3.2 Dynamic characteristics of the signaling cascade shown in Figure 3.15.

Compound	Integral, I_i	Maximum, X_i^{max}	Time (X_i^{max}), t_i^{max}	Characteristic time, τ_i	Signal duration, ϑ_i	Signal amplitude, A_i
X_1	0.797	0.288	0.904	2.008	1.458	0.273
X_2	0.695	0.180	1.871	3.015	1.811	0.192
X_3	0.629	0.133	2.855	4.020	2.109	0.149

信号通路的交联 (crosstalk)



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信号通路的交联 (crosstalk)

Crosstalk measure：

$$C = \frac{X_{\text{extrinsic}}}{X_{\text{intrinsic}}} = \frac{X_{\mathrm{T_A}}(\beta)}{X_{\mathrm{T_A}}(\alpha)}$$

Fidelity：

$$F = \frac{X_{T_A}(\alpha) / X_{R_A}(\alpha)}{X_{T_A}(\alpha) / X_{R_B}(\beta)}$$

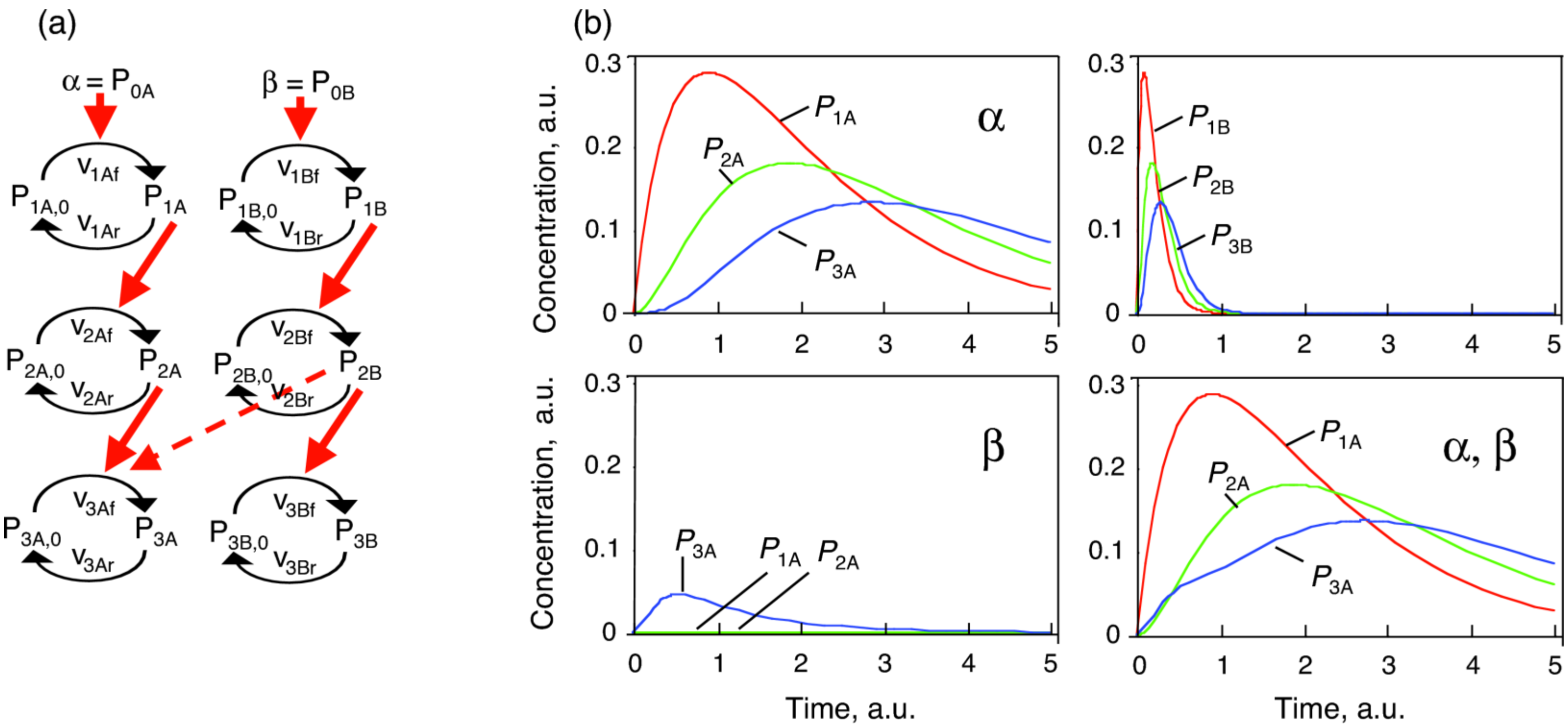
Intrinsic sensitivity &
Extrinsic sensitivity:

$$S_i(A) = \frac{X_{\mathrm{T_A}}(\alpha)}{X_{\mathrm{T_A}}(\alpha,\beta)} \quad \text{and} \quad S_e(A) = \frac{X_{\mathrm{T_A}}(\beta)}{X_{\mathrm{T_A}}(\alpha,\beta)}$$

Si > 1, Se > 1: Mutual signal inhibition; Si > 1 , Se < 1: Dominance of intrinsic signal;
Si < 1, Se > 1: Dominance of extrinsic signal; Si < 1, Se < 1: Mutual signal amplification.

信号通路的交联 (crosstalk)

例如：



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Crosstalk of MAP kinase pathways. Pathway A leads to activation of P_{3A} upon stimulation by α, pathway B transmits signal from β to P_{3B}. Crosstalk occurs through signaling from P_{2B}. Dynamics of pathways A and B upon stimulation by α, β, or both (as indicated). $k_{iAf} = k_{iAr} = 1$; $k_{iBf} = k_{iBr} = 10$

信号通路的交联 (crosstalk)

Table 3.4 Crosstalk measures for the pathway in Example 3.3.

	X_A (α)	X_A (β)	X_A (α, β)	$S_i(A) = \frac{X_A(\alpha)}{X_A(\alpha,\beta)}$	$S_e(A) = \frac{X_A(\beta)}{X_A(\alpha,\beta)}$	$C = \frac{X_A(\beta)}{X_A(\alpha)}$
$I_3 = \int_0^\infty P_{3A}(t)dt$	0.628748	0.067494	0.688995	0.912557	0.09796	0.107347
$t_{P_{3A}}^{\max}$	2.85456	0.538455	2.73227	1.04476	0.197072	0.18863
$\text{Max}(P_{3A})$	0.132878	0.0459428	0.136802	0.971314	0.335833	0.345752