



系统生物学 (Systems Biology)

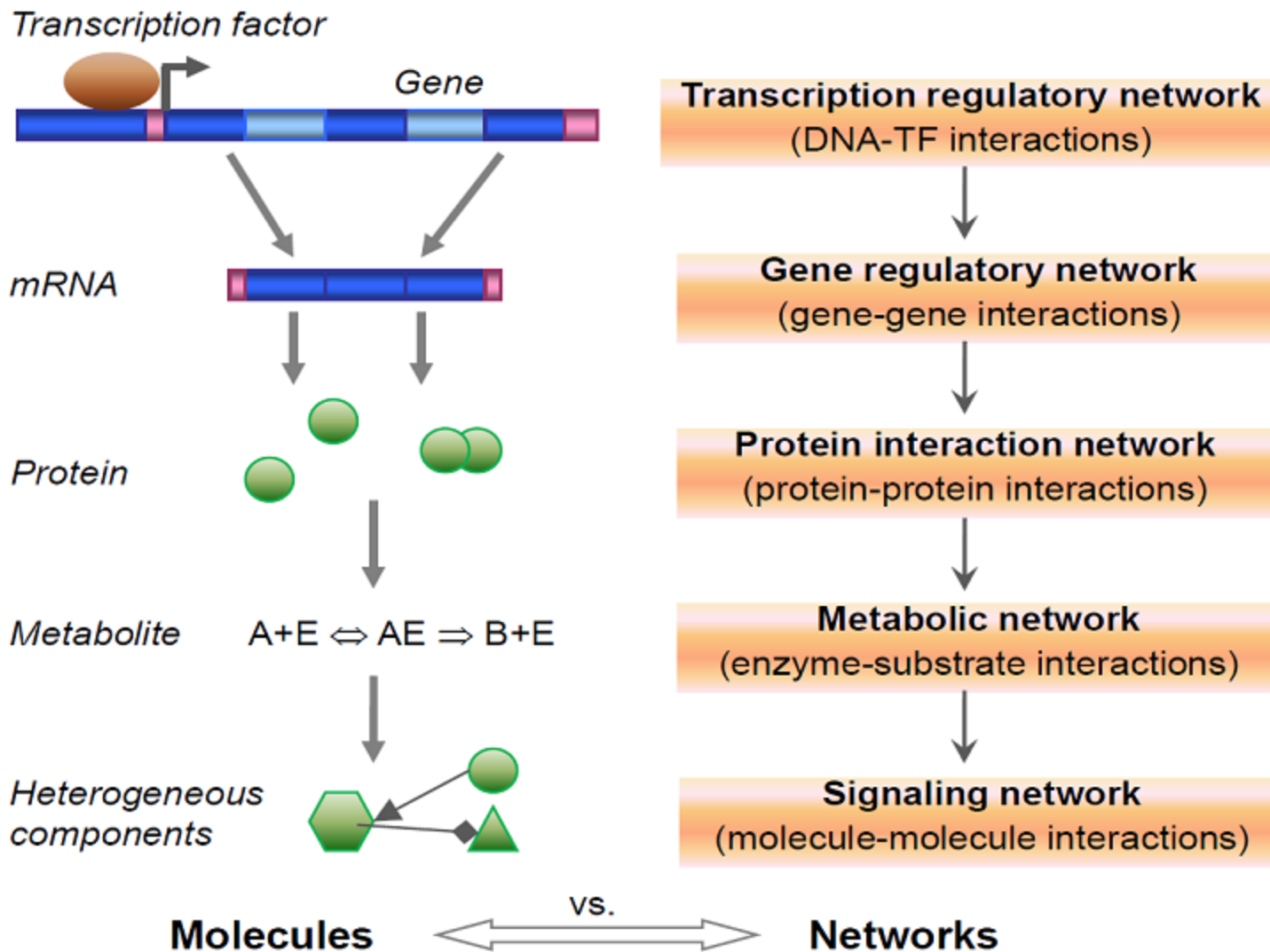
马彬广



转录调控网络模体

(第六讲)

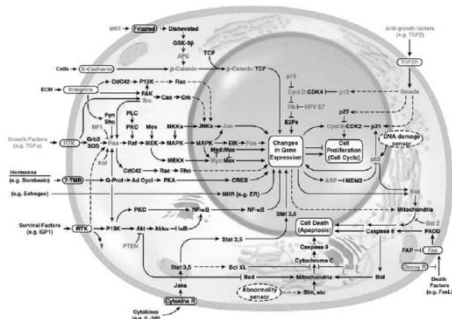
Biomolecular Networks ?



Central Dogma of Biology



转录调控作用



(a)

Transcription factor



Transcription



TF binding site
(cis-regulatory element)

Target gene

(b)

Transcription factor
(node)



Regulatory
interaction
(directed edge)

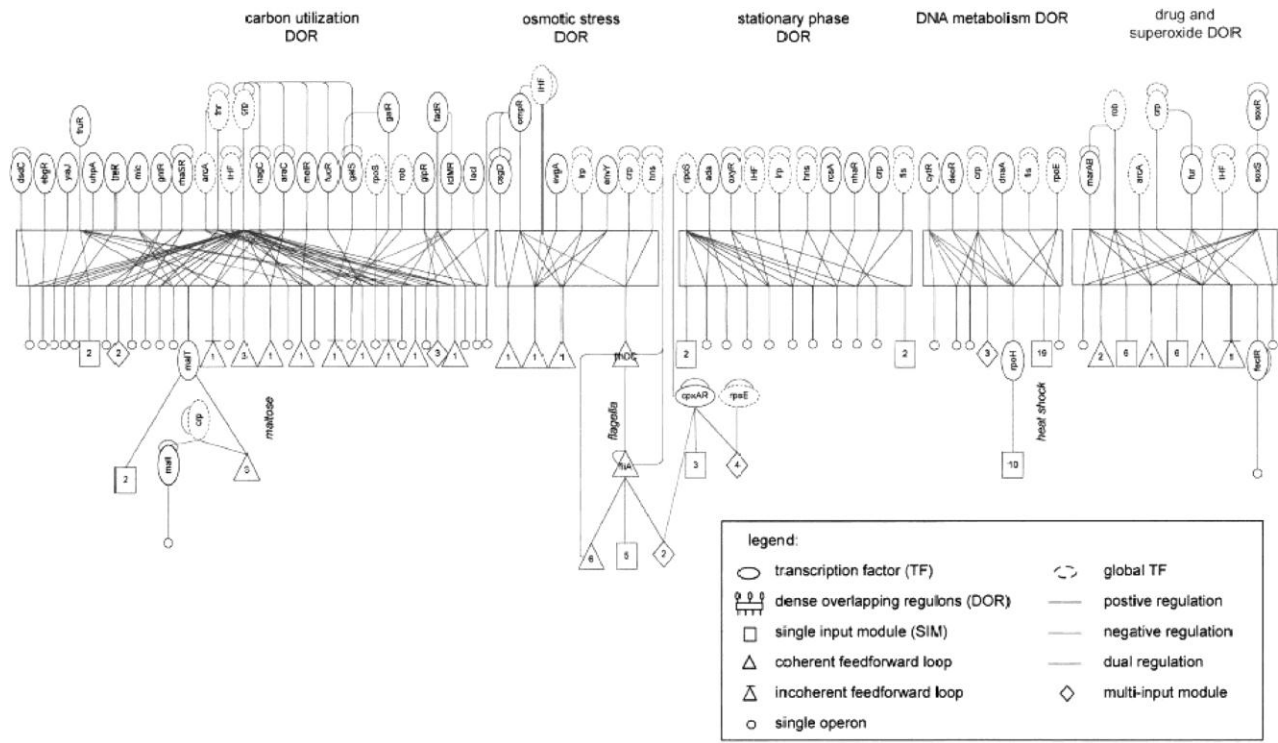


Target gene
(node)

Fig. 2.1. Transcriptional regulatory interaction. (a) Standard view: regulation of gene expression is mediated by transcription factors that bind DNA through their DNA-binding domain. The specific DNA sequence to which they bind is called a TF binding site or cis-regulatory element. Binding to the cis-regulatory element may either activate or repress the transcription of a nearby target gene (black box). The arrow head represents the transcriptional start site. (b) Network view: transcription factors and target genes are represented as nodes and a directed link connecting a transcription factor to a target gene represents a regulatory interaction between the two.



大肠杆菌转录调控网络

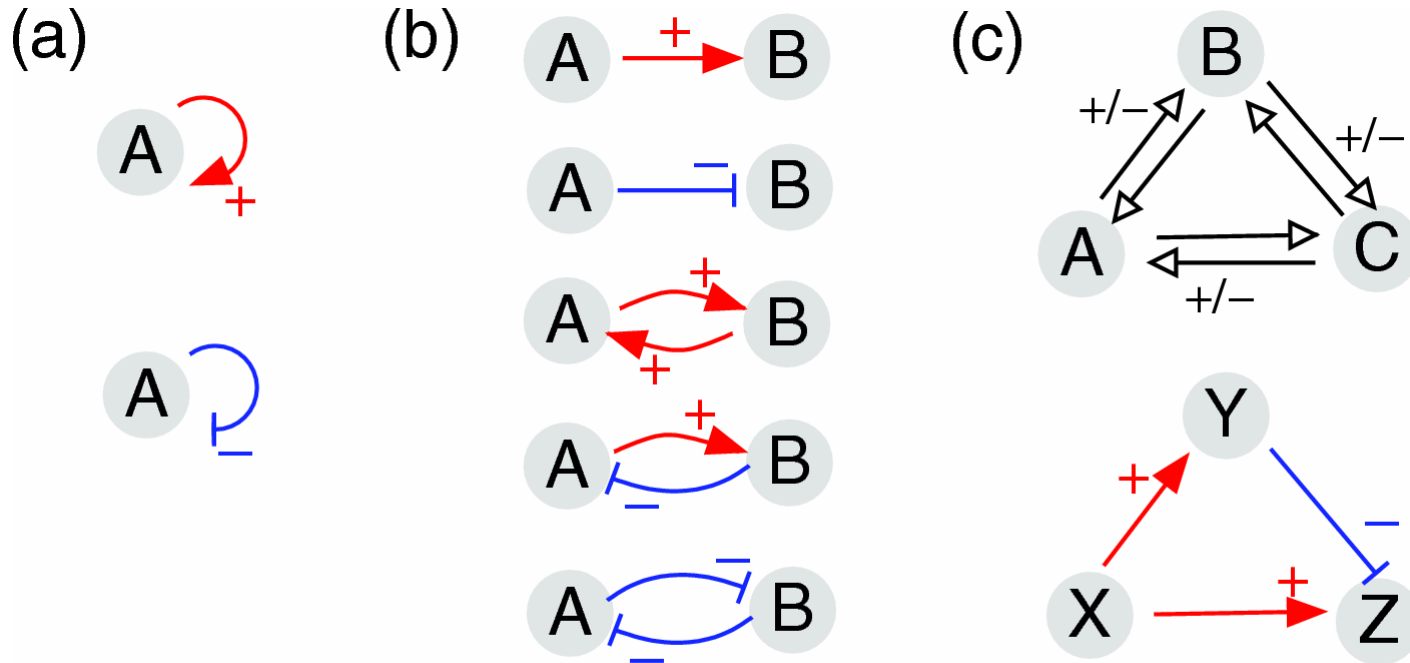


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In this arrangement, functional subsystems of the network become visible. The network consists of several large blocks related to different cell functions, and information is processed from the top to the bottom. Feed-forward loops in the output layer are marked by triangles. Unlike in the other figures – activation is shown in blue and repression in red. From Shen-Orr *et al.* (Nature Genetics 31, 64-68)



基本调控模式



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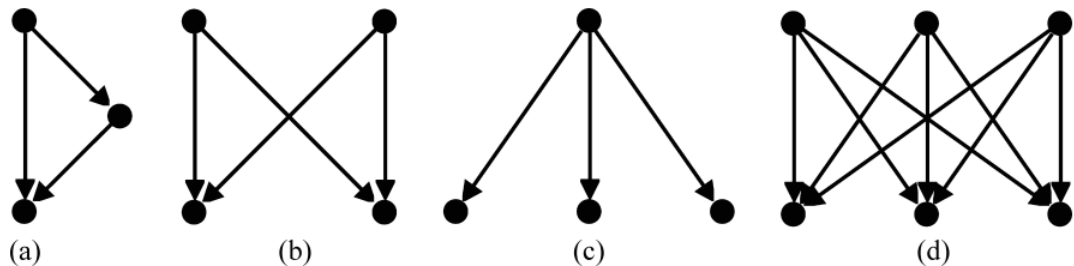
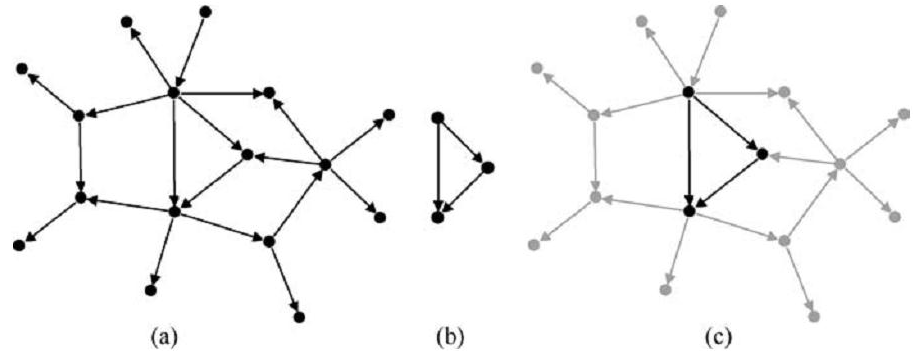
Basic regulatory patterns with one, two, or three nodes. (a) Positive (red) and negative (blue) autoregulation. (b) Two-node patterns. (c) Three-node patterns can contain up to six arrows. By selecting three arrows and signs, one obtains the incoherent feed-forward loop type I, which appears as a network motif in transcription networks.



网络模体 (Network Motif) 的概念

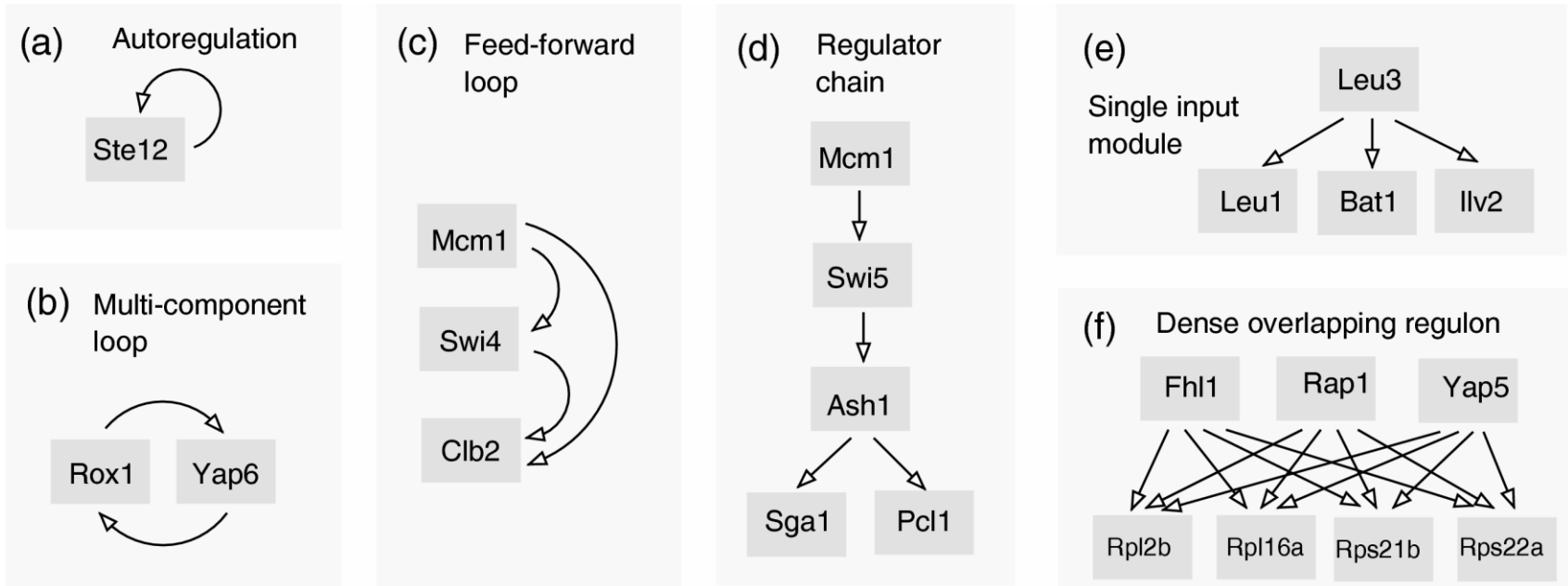


- 概念：复杂网络中频繁出现的连接模式。
- 所谓“频繁”，是指相比于随机网络显著地多。
- 网络模体的定义体现“相对性”和“非随机性”。
- 网络模体是网络功能的基本单位。如果把网络比喻成一个分子，则网络模体则是相应的原子（类比元素周期表）。
- 转录调控网络模体反映基因调控的基本模式。





酵母转录网络中的Motif



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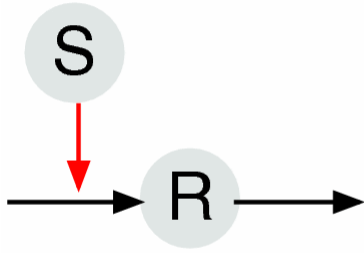
Network motifs in the transcription network of the yeast *S. cerevisiae*. Gene names refer to specific examples in the network. Redrawn from Lee *et al.* (Science 298, 799-804)



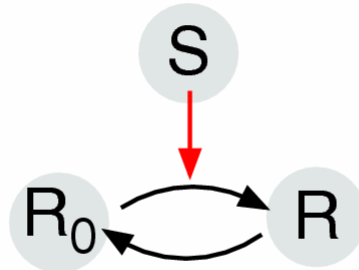
单调控箭头及其稳态响应



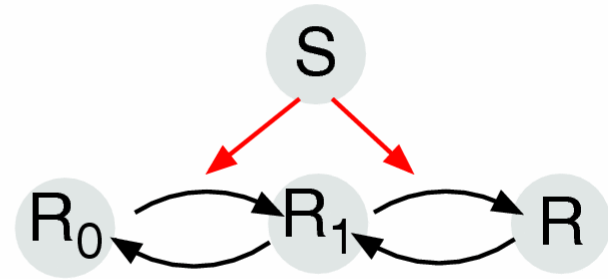
(a)



(b)



(c)



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Possible regulation patterns behind a simple activation $S \rightarrow R$. (a) Linear pattern: a substance S (“signal”) regulates the production of R (“response”). (b) In a loop pattern (e.g., in a phosphorylation cycle), S converts inactive R_0 into its active form R . (c) In a double-loop pattern (e.g., double phosphorylation), two steps are necessary to activate R . Black arrows indicate chemical reactions, while red and blue arrows denote activation and inhibition, respectively.

Response rate equation:
$$\frac{dr}{dt} = f(s, r)$$

Steady state response:

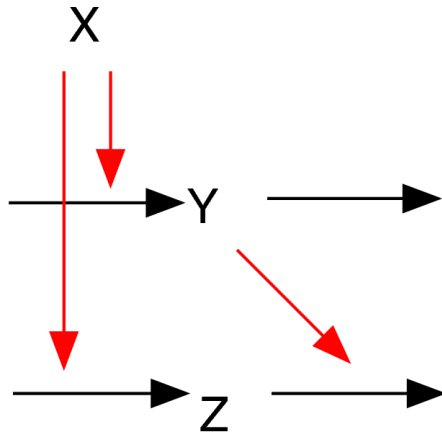
$$f(s, r) = 0 \Rightarrow r^{st}(s)$$



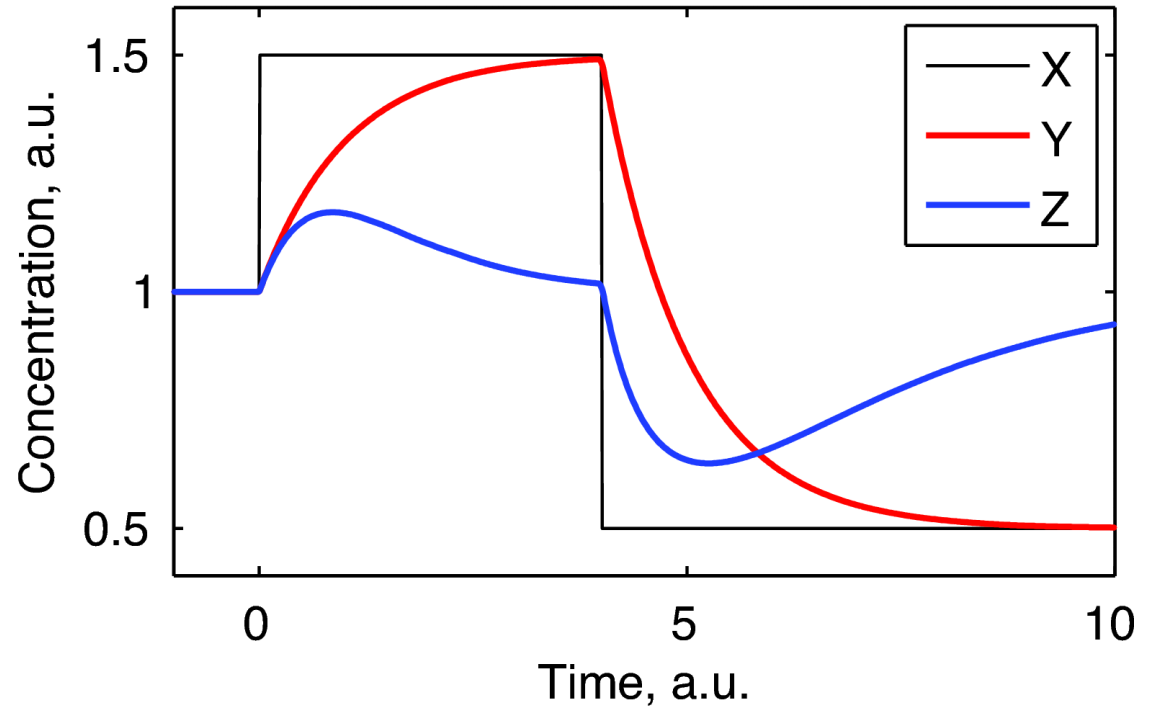
Adaptation Motif



(a)



(b)



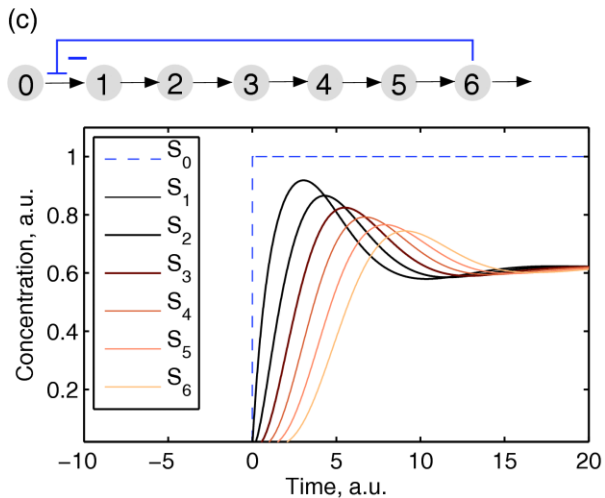
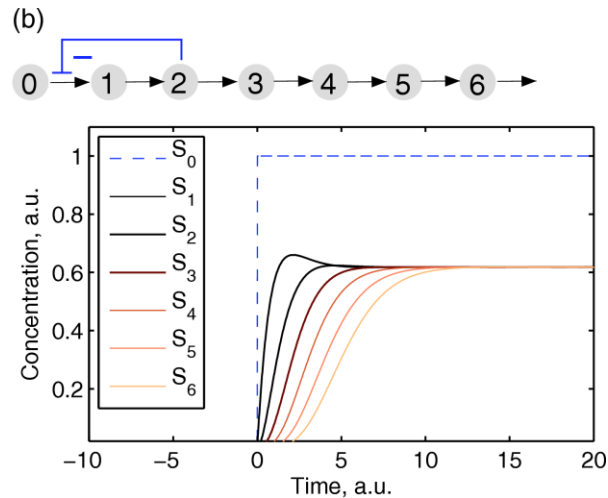
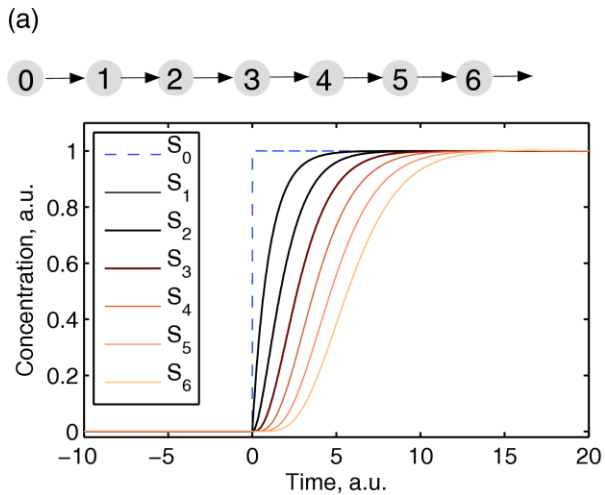
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Dynamics:
$$\begin{cases} \frac{dy}{dt} = \alpha_y x - \beta_y y \\ \frac{dz}{dt} = \alpha_z x - \beta_z yz \end{cases}$$
 for $x > 0$, the steady state, $y^{st} = \frac{\alpha_y}{\beta_y} x$, $z^{st} = \frac{\alpha_z \beta_y}{\beta_z \alpha_y}$

The steady state level of Z depends only on the kinetic constants.



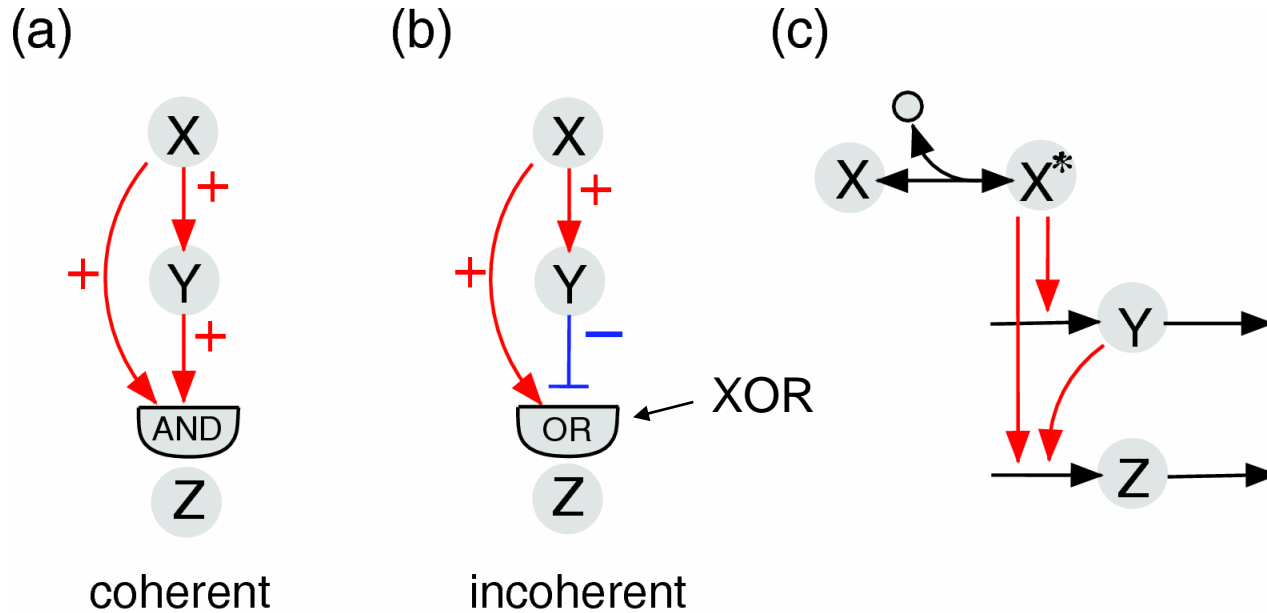
Negative FeedBack



Negative feedback in an unbranched metabolic chain. (a) Concentration time series in a chain of six reactions (shown on top) after external substrate (---) becomes available ($s_0 = 1$) at time $t = 0$. (b) Negative feedback by the second metabolite decreases the steady-state level and speeds up the response. (c) Negative feedback from the last metabolite leads to an overshoot and damped oscillations. All parameters k_i have a value of 1.



Feed-Forward Loops



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The input gene X regulates the output gene Z directly and *via* an intermediate gene Y. (a) Coherent feed-forward loop type 1 with AND gate. (b) Incoherent feed-forward loop type 1 with OR (should be XOR) gate. (c) Simple model of a feed-forward loop in transcription networks. The regulatory arrows represent transcriptional regulation of Y and Z; transcription and translation are modeled by a single step. X is activated by rapid ligand binding (circle denotes the ligand, X*; the active form). Red, blue, and black arrows indicate activation, inhibition, and reactions, respectively.



Dynamic model of the Feed-Forward Loop



$$\begin{cases} \frac{dy}{dt} = f_y(x) - \beta_y y \\ \frac{dz}{dt} = f_z(x, y) - \beta_z z \end{cases}$$

Step-like gene input function for the transcription of gene Y:

$$f_y(x) = \alpha_y \Theta(x > x_0)$$

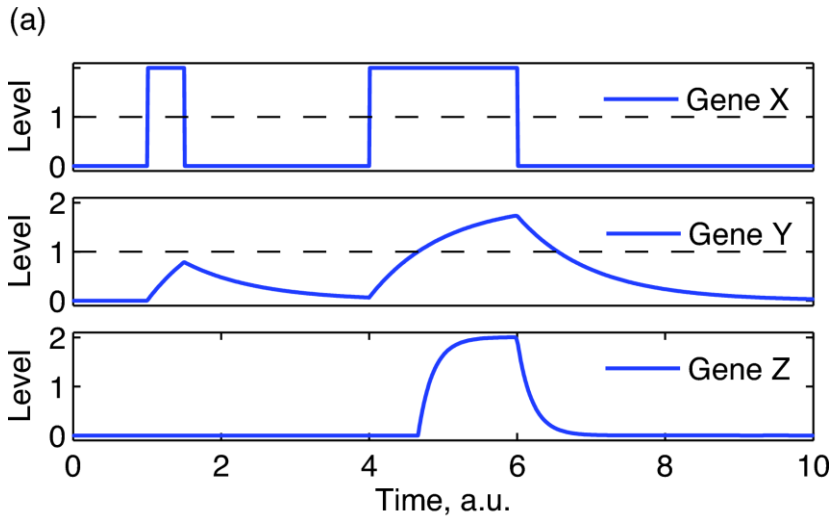
Input function for gene Z:

coherent, AND: $f_z(x, y) = \alpha_z \Theta(x > x_0 \text{ AND } y > y_0)$

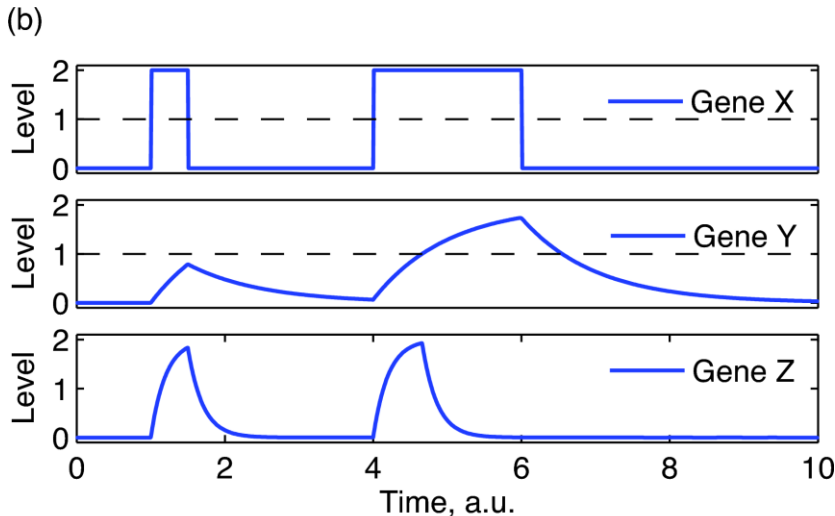
incoherent, AND: $f_z(x, y) = \alpha_z \Theta(x > x_0 \text{ XOR } y > y_0)$



Dynamic Behaviors



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Dynamic behavior of two types of feed-forward-loop (FFL). (a) Coherent FFL type 1 with AND logic. Time curves for active input X (top), intermediate gene Y (center), and output Z (bottom) are shown (arbitrary units). The FFL filters out the short pulse; the response to the longer pulse is delayed, but the response to the end of the pulse is immediate. (b) Incoherent FFL type 1 with OR (should be XOR) logic. The onset of each input pulse leads to a pulse of Z of fixed maximal length. Model parameters $\alpha_y = 2$, $\beta_y = 1$, $\alpha_z = 10$, $\beta_z = 5$.



网络模体分析软件



- ❑ Mfinder: a software tool for network motif detection in directed and undirected networks. It computes the number of occurrences of a motif of restricted size in the target network and a uniqueness value, which is a lower bound for the frequency of concept.
- ❑ MAVisto: a tool for the exploration of motifs in biological networks combining a flexible motif search algorithm and different views for the analysis and visualization of network motifs.
- ❑ FANMOD: a relatively recent tool for network motif detection in directed and undirected networks and is based on an improved algorithm that outperforms the existing tools Mfinder and MAVisto in the task of network motif detection. In contrast to Mfinder and MAVisto, the FANMOD tool detects only motifs that are induced subgraphs whereas the other two discover all supported motifs. FANMOD supports the analysis of vertex-labeled and/or edge-labeled networks.
- ❑ 通用网络分析软件: Pajek, Osprey, Cytoscape (Plugins MCODE, NeMo).