



INSTITUTE OF NEUROSCIENCE

中国科学院神经科学研究所

# Genomics

Jun Yan

**Laboratory of Network Computation  
Institute of Neuroscience  
Chinese Academy of Sciences**

# 基因组

- 一个基因组 (genome) 是指一种生物体中的整套遗传信息，一般为一个受精卵或一个体细胞的细胞核中所有DNA分子的总和。如植物有核基因组、线粒体基因组和叶绿体基因组。
- 基因组学研究通常包括：基因组作图，基因组测序，基因组注释，基因功能鉴定等

## 功能基因组学 (functional genomics)

利用结构基因组学研究所得的各种来源的信息，建立与发展各种技术和实验模型来测定基因及基因组非编码序列的生物学功能

## 比较基因组学 (comparative genomics)

通过模式生物基因组之间或模式生物基因组与人类基因组之间的比较与鉴别，为研究生物进化和分离人类遗传病的候选基因以及预测新的基因功能提供依据。其中，着重研究生物进化的领域亦称为进化基因组学 (evolutionary genomics)

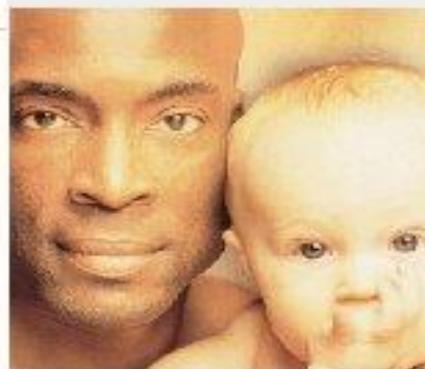
# Science magazine

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SEARCH BROWSE ▶ ORDER AN ARTICLE

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16 February  
2001  
Volume 291  
Number 5507

## The Human Genome



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**Research**

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### NEW THIS WEEK:

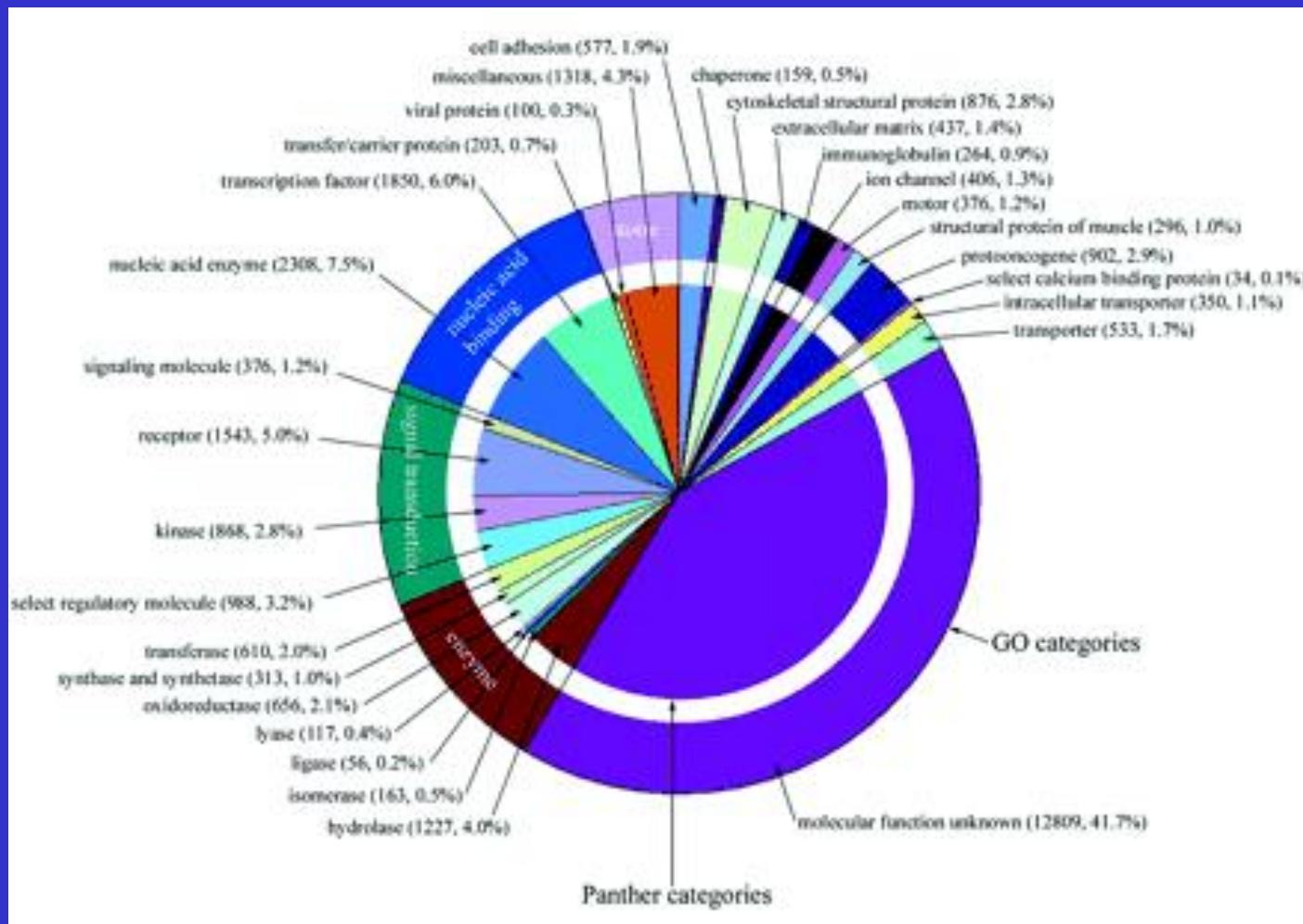
**Human Genome Special Issue:  
*Free Access to All Users***

**[Editorial Overview](#)**

**[The Human Genome Sequence](#)**

**[The Story Behind the Genome \(with Timeline\)](#)**

**[How to Access the Data](#)**



26383条人类基因分子功能的分布

# Comparative Genomics

## MAMMALIAN RADIATIONS

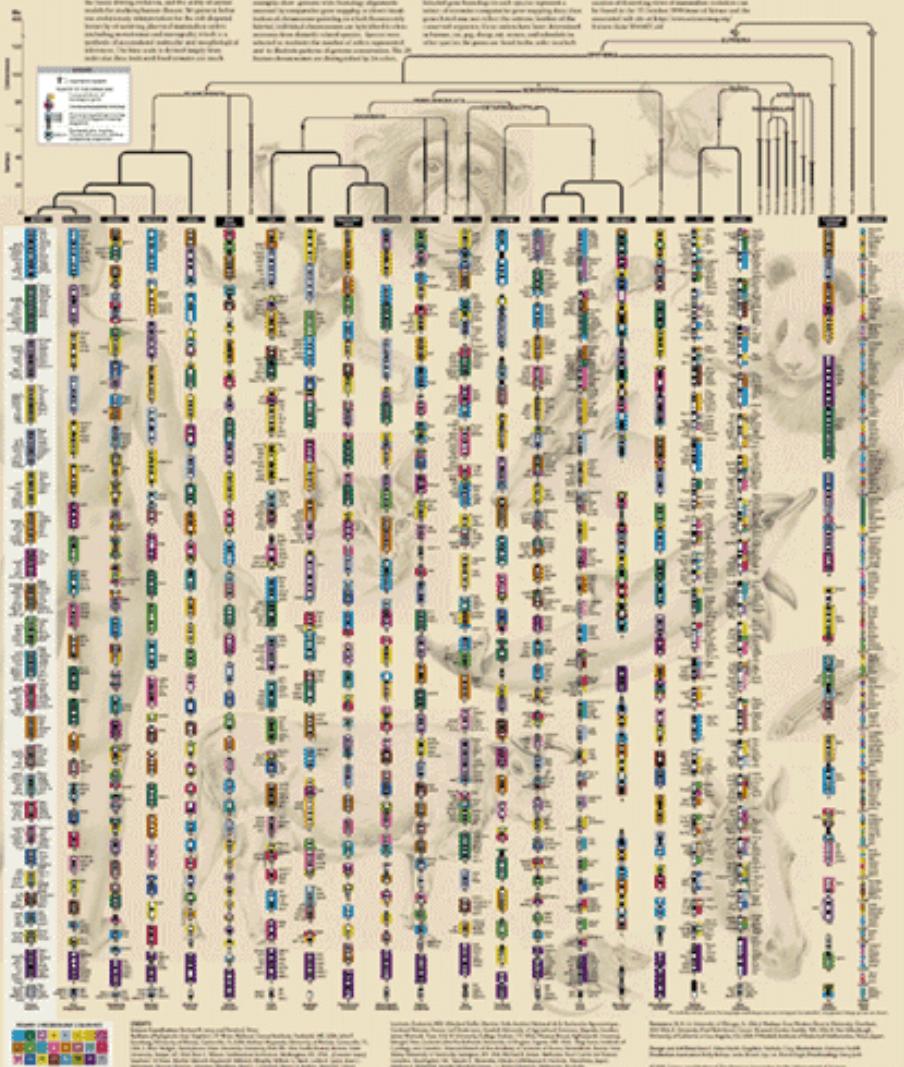
biological evolutionary history seems to have knowledge and little energy to offer in a gene's life.

program writing guidelines around the process of all medical encounters. Weights of the physiognomy test digitized programs for 21 representative species from 11 genera, which are distributed on the website. These programs were used to generate 1000 images of each species, which were then used to train a logistic regression model to predict species correctly in a field. Morphometric characteristics pertaining to a field thoroughly informed the design of the programs. The programs were then distributed among species experts to evaluate the number of errors committed and to facilitate pairwise diagnostic communication. We also conducted a survey among fieldworkers by e-mail.

of the observed heterogeneity is due to differences in the number of neurons per sample, as the mean number of interneurons per sample was significantly higher in the hippocampus than in the cortex (Table 1). The hippocampus had more interneurons per sample than the cortex, suggesting that the hippocampus may have a greater capacity for generating interneurons than the cortex. In addition, the hippocampus had more interneurons per sample than the amygdala, suggesting that the hippocampus may have a greater capacity for generating interneurons than the amygdala.

Maps Ten

X Genome Maps Ten



### **Research Genetics.**

**Microtire Double Diamond® Radial** Microtire Double Diamond® Radial is a tire designed for light-duty commercial vehicles. It features a deep, directional tread pattern designed to provide excellent grip and handling in wet and dry conditions. The tire is made from high-quality materials and is designed to last longer than standard tires. It is available in various sizes and load capacities to fit different types of vehicles.

# 基因和基因组

基因组大小 (bp)

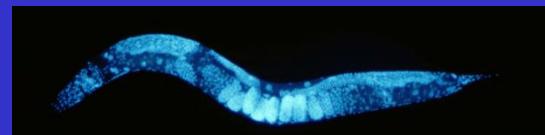
$1.4 \times 10^7$



$1 \times 10^8$



$1 \times 10^8$



$3 \times 10^9$



基因数量

6,000

12,000

19,000

35,000

## 人和若干模式生物的基因组大小

生物	估计基因组大小 (bp)	估计基因数目	平均基因密度(bp)
人 ( <i>Homo sapiens</i> )	$3 \times 10^9$	~ 30000	$10^5$
小鼠 ( <i>Mus musculus</i> )	$3 \times 10^9$ $4 \times 10^4$	> 80000	<
黑腹果蝇 ( <i>Drosophila melanogaster</i> )	$1.8 \times 10^8$	13601	1378
拟南芥 ( <i>Arabidopsis thaliana</i> )	$1 \times 10^8$	~ 25000	4000
秀丽隐杆线虫 ( <i>Caenorhabditis elegans</i> )	$9.7 \times 10^7$	19099	5079
酿酒酵母 ( <i>Saccharomyces cerevisiae</i> )	$1.2 \times 10^7$	6034	2005
大肠杆菌 ( <i>Escherichia coli</i> )	$4.67 \times 10^6$	4288	1090
流感嗜血杆菌 ( <i>Haemophilus influenzae</i> )	$1.8 \times 10^6$	1749	1030

### Effective population size x Nucleotide mutation rate ( $N_e u$ )

**A**

*Prochlorococcus*  
*Tetrahymena thermophila*  
*Salmonella enterica*  
*Legionella pneumophila*  
*Helicobacter pylori*  
*Neisseria meningitidis*  
*Escherichia coli*  
*Vibrio cholerae*  
*Enterococcus faecium*  
*Cryptococcus neoformans*  
*Campylobacter jejuni*  
*Cryptosporidium parvum*  
*Saccharomyces cerevisiae*  
*Chlamydomonas reinhardtii*  
*Dictyostelium discoideum*  
*Neurospora crassa*  
*Streptococcus pyogenes*  
*Pseudomonas aeruginosa*  
*Giardia lamblia*  
*Toxoplasma gondii*  
*Trypanosoma cruzi*  
*Leishmania donovani*  
*Drosophila* sps.  
*Encephalitozoon cuniculi*  
*Artemia franciscana*  
*Zea mays*  
*Caenorhabditis* sps.  
*Arabidopsis thaliana*  
*Ciona intestinalis*  
*Silene* sps.  
*Crassostrea virginica*  
*Anopheles* sps.  
*Strongylocentrotus franciscanus*  
*Pinus sylvestris*  
*Fugu rubripes*  
*Hordeum vulgare*  
*Plasmodium falciparum*  
*Oryza sativa*  
*Ficedula* sps.  
*Oncorhynchus tshawytscha*  
*Pan troglodytes*  
*Homo sapiens*  
*Mus musculus*

0.00      0.04      0.08      0.50      1.00



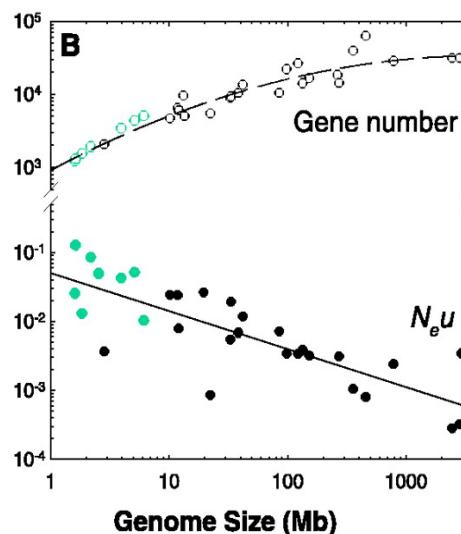
Prokaryotes

Unicellular eukaryotes

Invertebrates

Vascular plants

Vertebrates



(A) Estimates of the composite parameter  $N_e u$  for a phylogenetically diverse assemblage of species. (B) The relationship between estimated  $N_e u$ , total gene number, and genome size. Data for prokaryotes are plotted in blue. The log-log regression of  $N_e u$  versus genome size is highly significant, with an intercept of  $-1.30 \pm 0.40$ , a slope of  $-0.55 \pm 0.07$ , and  $r^2 = 0.659$ ,  $df = 28$ . The number of species plotted differs between graphs because genome structure information is not available for all species with  $N_e u$  estimates.

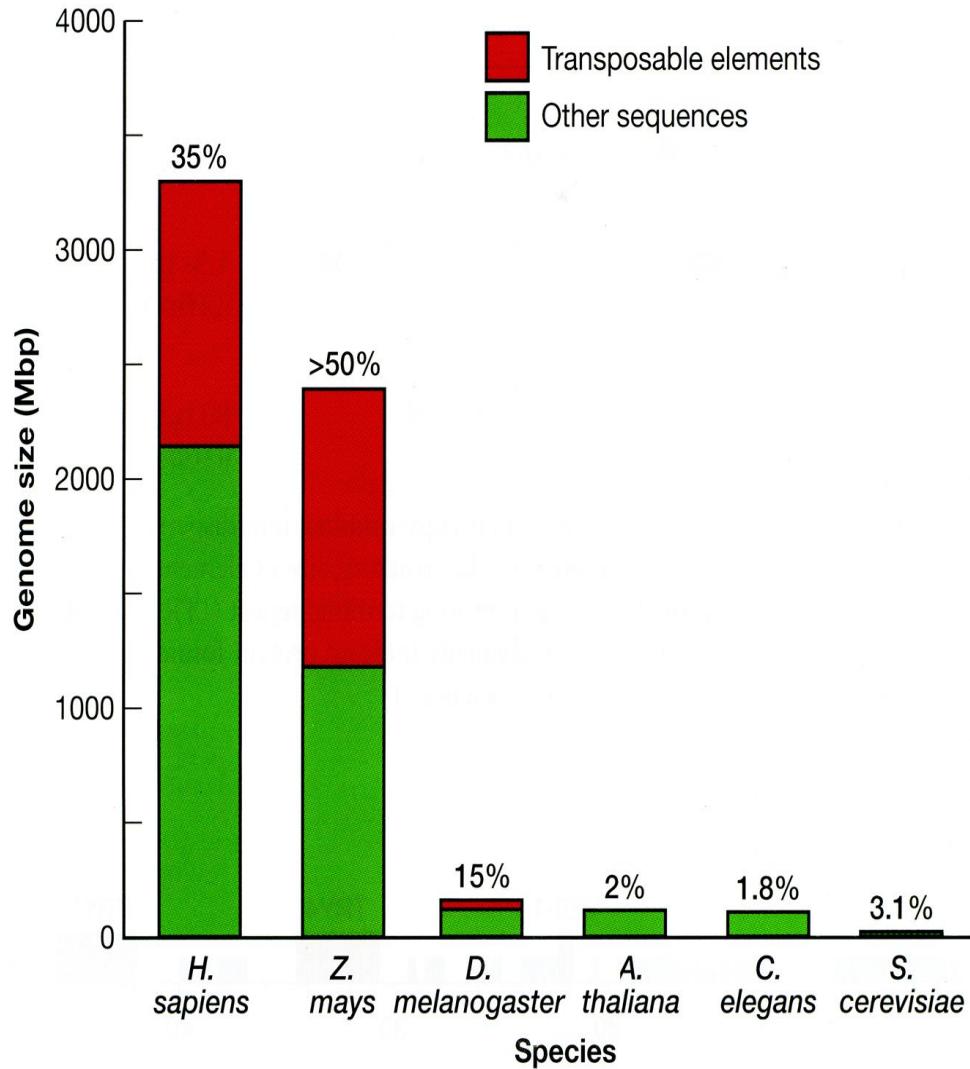
*The Origins of Genome Complexity*

Science 302: 1401-1404 . 11/21/2003

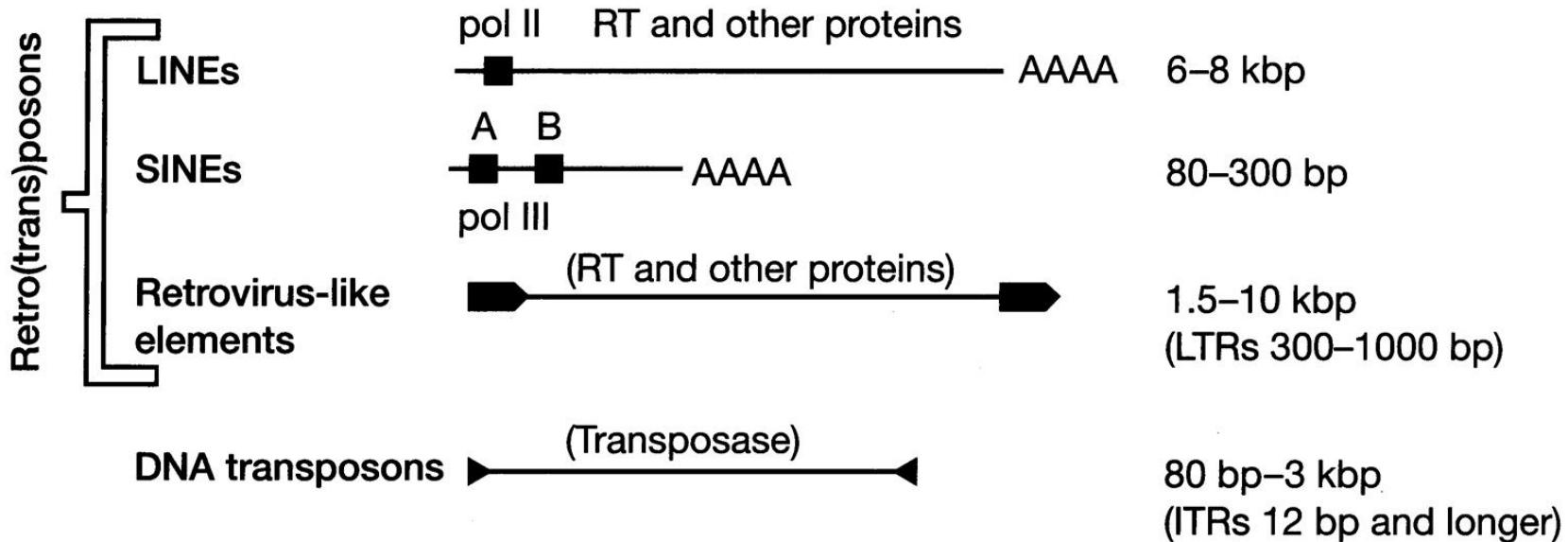
# 基因组进化

- 基因组排列 (genome arrangement): 是指基因序列的变化 (序列插入, 转座等)
- 基因组含量 (genome content): 基因的获得 (序列的趋异、复制、重组、水平转移) 和基因丢失

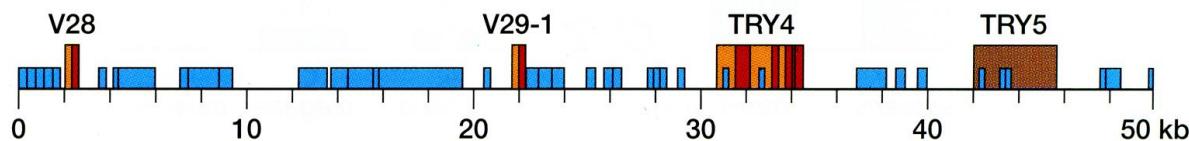
# Transposable elements



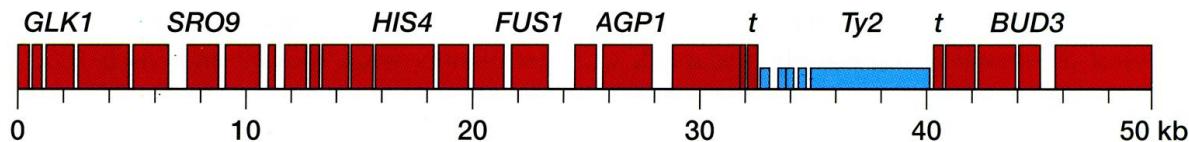
# Transposable elements



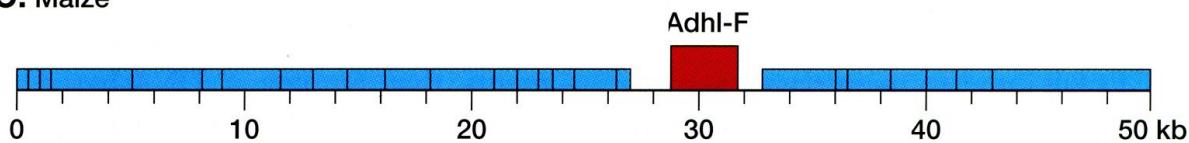
**A. Human**



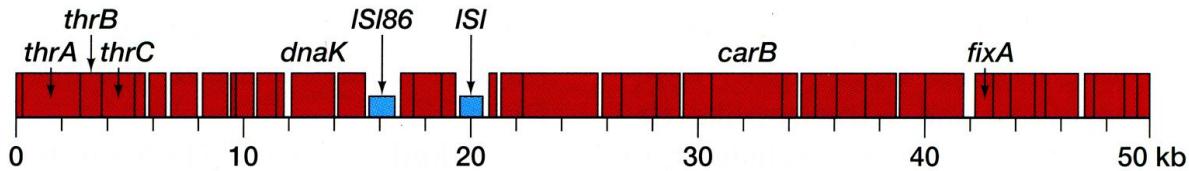
**B. *Saccharomyces cerevisiae***



**C. Maize**



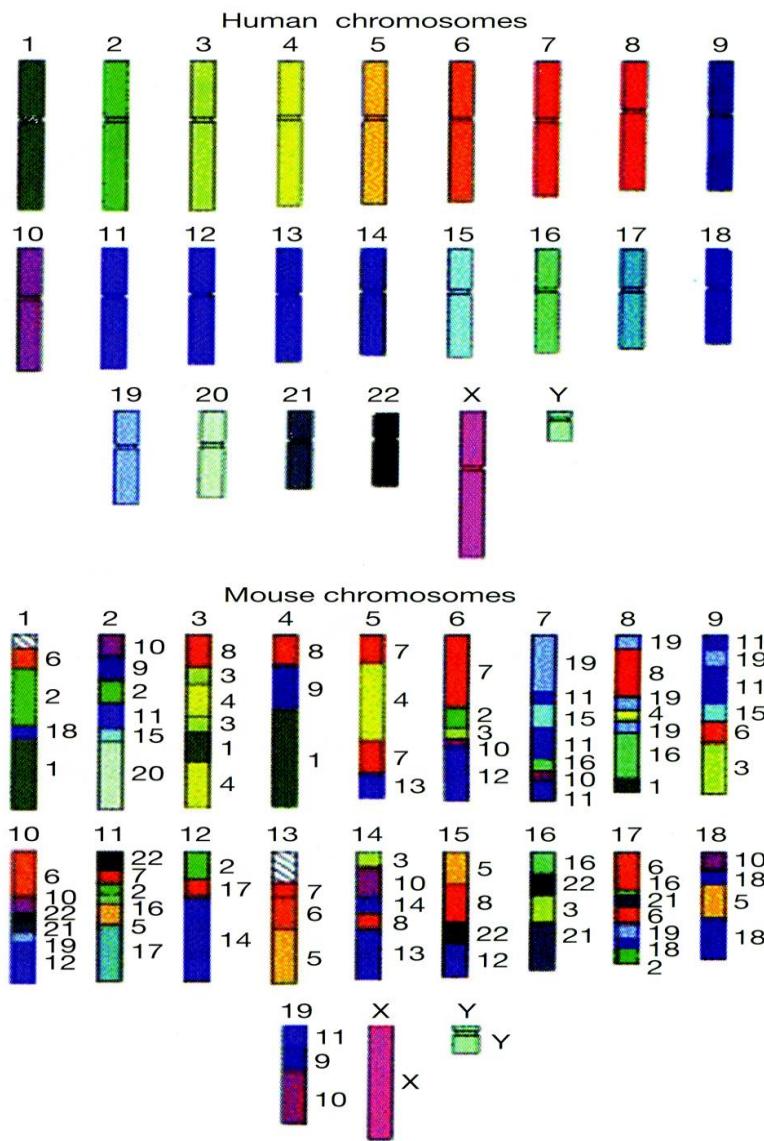
**D. *Escherichia coli***



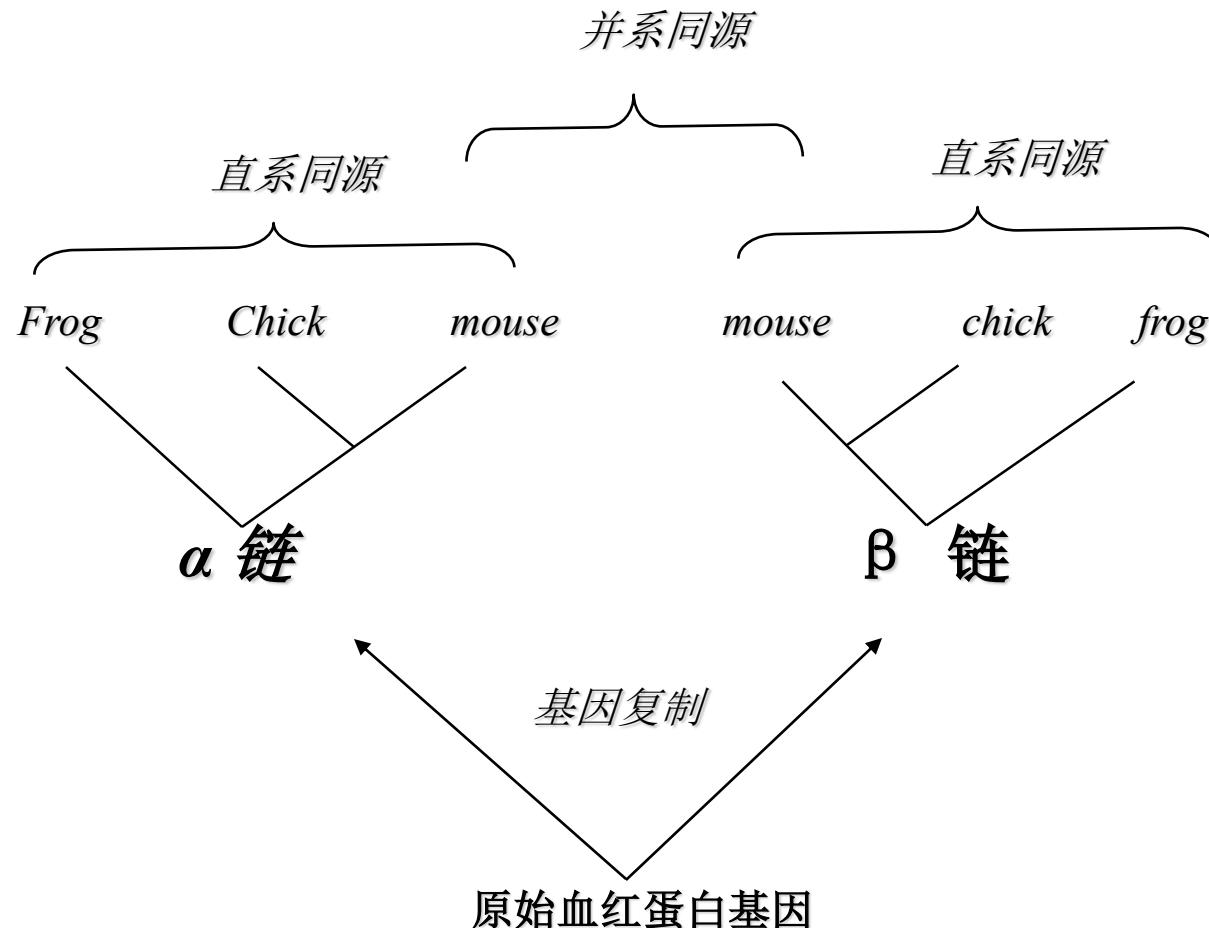
**KEY**

Gene      Intron      Human pseudogene      Genome-wide repeat      t tRNA gene

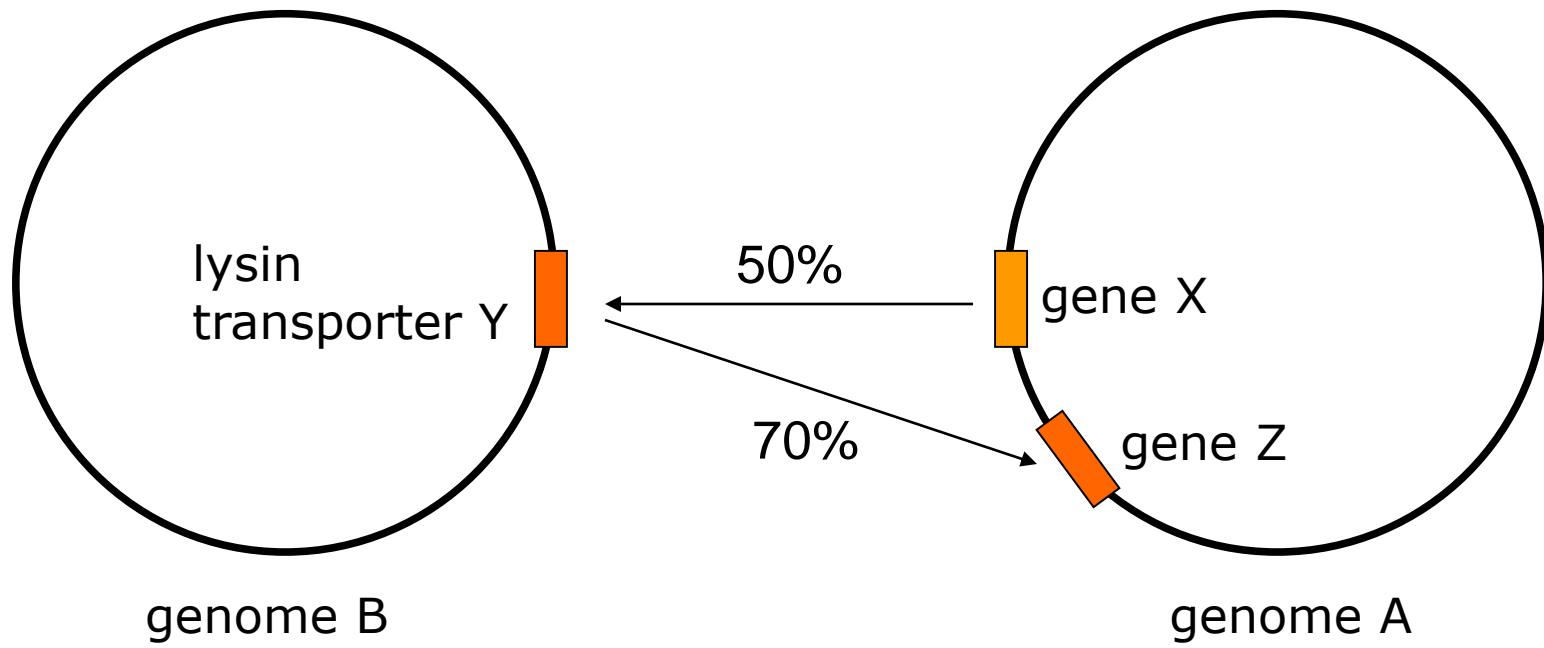
# Gene Rearrangement



# 直系同源和并系同源基因



## 直系 / 并系



**gene Z ⇄ gene Y : orthologs**  
**gene X ⇄ gene Y : homologs**  
**gene X ⇄ gene Z : paralogs**

## 直系同源体簇(COG)

直系同源基因(orthologous gene)是指在不同物种之间同源相似的基因，而并系同源基因(paralogous gene)是指一个物种内的同源基因。一个生物物种的基因组中，两个基因或开放读码在各自全长的60%以上范围内，同一性不少于30%时，称为同源体。研究直系同源基因之间或并系同源基因之间的功能关系，可以为基因组分析提供很大的帮助。

例如，比较8个已完成测序的整个基因组所编码的蛋白质序列，可以发现代表不同系统发育关系并反映了不同物种的直系同源体簇(cluster of orthologous groups, COG)。

COG - Microsoft Internet Explorer

文件(F) 编辑(E) 查看(V) 收藏(A) 工具(T) 帮助(H)

地址(D) http://www.ncbi.nlm.nih.gov/COG/ 转到 链接

 NCBI

**COGs**  
Phylogenetic classification of proteins encoded in complete genomes

Clusters of Orthologous Groups of proteins (COGs) were delineated by comparing protein sequences encoded in 34 complete genomes, representing 26 major phylogenetic lineages. Each COG consists of individual proteins or groups of paralogs from at least 3 lineages and thus corresponds to an ancient conserved domain. Proteins from two eukaryotic genomes were assigned to COGs and can be reached from each individual COG page

[Science 1997 Oct 24;278\(5338\):631-7.](#)  
[Nucleic Acids Res 2000 Jan 1; 28\(1\):33-6.](#)  
[Nucleic Acids Res 2001 Jan 1; 29\(1\):22-28.](#)

[Help](#)

[COgnitor](#)

Protein/Gene name:

Text search:

Code	Name	Proteins in COGs	Principal component analysis of genomes
◆ A	<a href="#">Archaeoglobus fulgidus</a>	2420	1849
◆ O	<a href="#">Halobacterium sp. NRC-1</a>	2058	1404
◆ M	<a href="#">Methanococcus jannaschii</a>	1786	1320
◆ T	<a href="#">Methanobacterium thermoautotrophicum</a>	1873	1375
◆ P	<a href="#">Thermoplasma acidophilum</a>	1479	1176
◆ K	<a href="#">Pyrococcus horikoshii</a>	2080	1365
◆ K	<a href="#">Pyrococcus abyssi</a>	1767	1443
◆ Z	<a href="#">Aeropyrum permixtum</a>	2722	1169
◆ Y	<a href="#">Saccharomyces cerevisiae</a>	5954	2175
◆ Q	<a href="#">Aquifex aeolicus</a>	1560	1317
◆ V	<a href="#">Thermotoga maritima</a>	1858	1507
◆ D	<a href="#">Deinococcus radiodurans</a>	3194	2176
◆ R	<a href="#">Mycobacterium tuberculosis</a>	3924	2468
◆ B	<a href="#">Bacillus subtilis</a>	4118	2803
◆ C	<a href="#">Bacillus halodurans</a>	4066	2728
◆ C	<a href="#">Synechocystis</a>	3168	2113
◆ E	<a href="#">Escherichia coli</a>	4286	3327
◆ E	<a href="#">Buchnera sp. APS</a>	575	559
◆ F	<a href="#">Pseudomonas aeruginosa</a>	5567	4191
◆ G	<a href="#">Vibrio cholerae</a>	3834	2745
◆ H	<a href="#">Haemophilus influenzae</a>	1695	1504
◆ S	<a href="#">Xylella fastidiosa</a>	2766	1491
◆ N	<a href="#">Neisseria meningitidis</a>	2081	1455
	<a href="#">Ustilago maydis</a>	1570	1001

[List of COGs](#)

[Distribution](#)

[Co-occurrences](#)

[Phylogenetic patterns](#)

[Phylogenetic patterns search](#)

[Functional categories](#)

[J](#) [K](#) [L](#)

[D](#) [O](#) [M](#) [N](#) [P](#) [T](#)

[G](#) [C](#) [E](#) [F](#) [H](#) [I](#)

[R](#) [S](#)

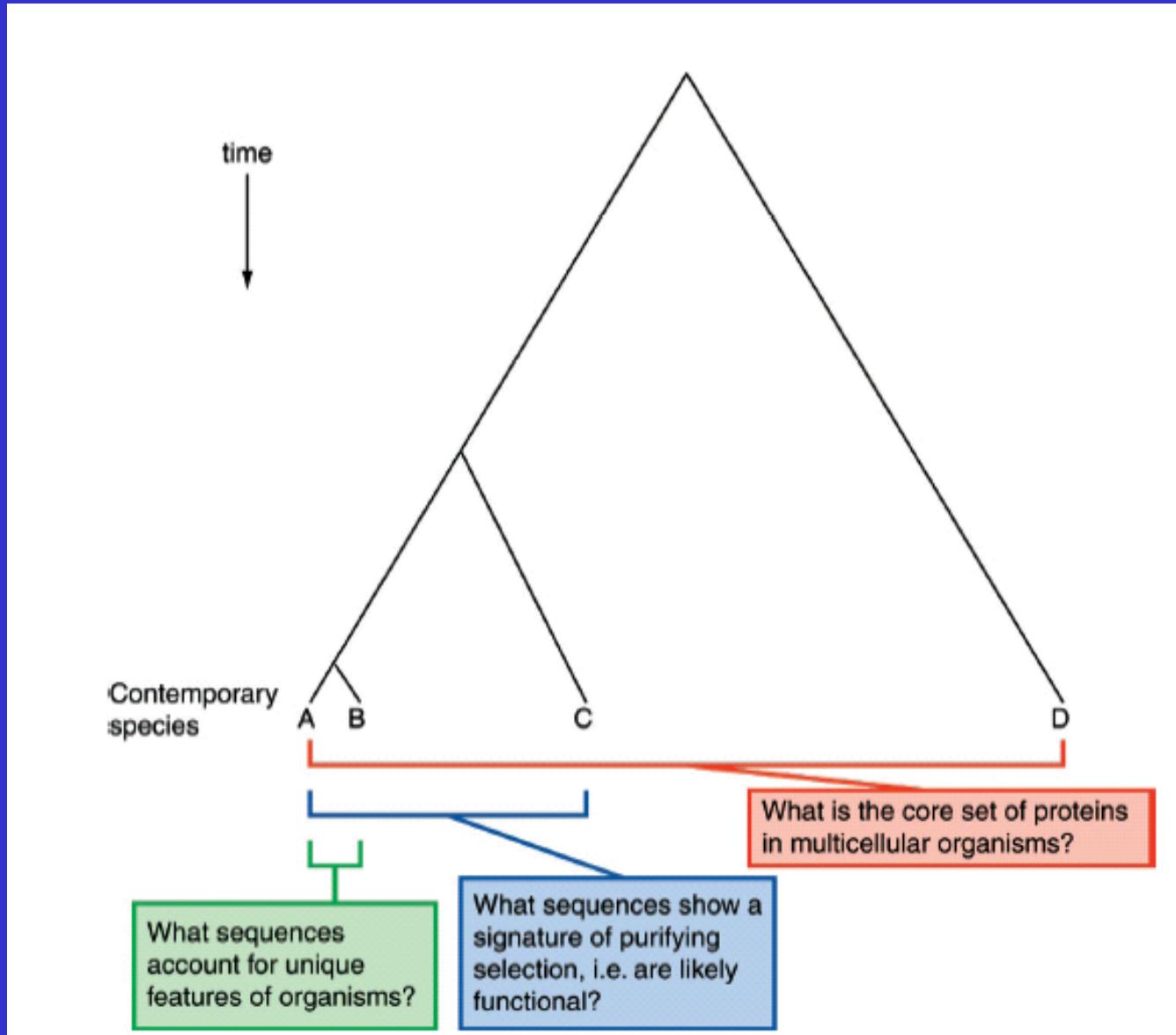
[Pathways and functional systems](#)

[FTP](#)

# NCBI COG网页

(<http://www.ncbi.nlm.nih.gov/COG/>)

# 比较基因组学不同分析水平的不同问题





哈佛大学阿布扎诺夫博士与普林斯顿大学格兰特教授夫妇

Vol 442 | 3 August 2006 | doi:10.1038/nature04843

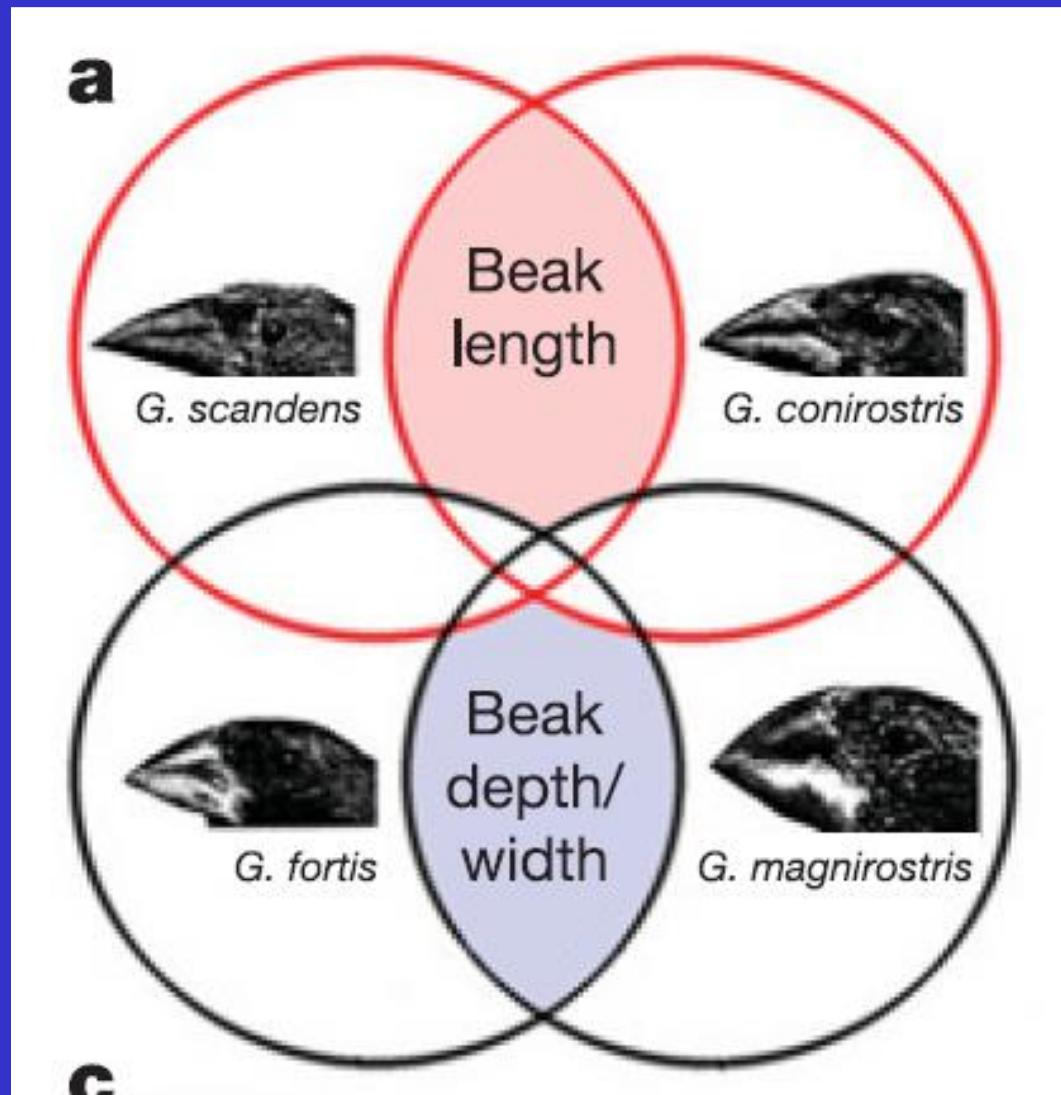
nature

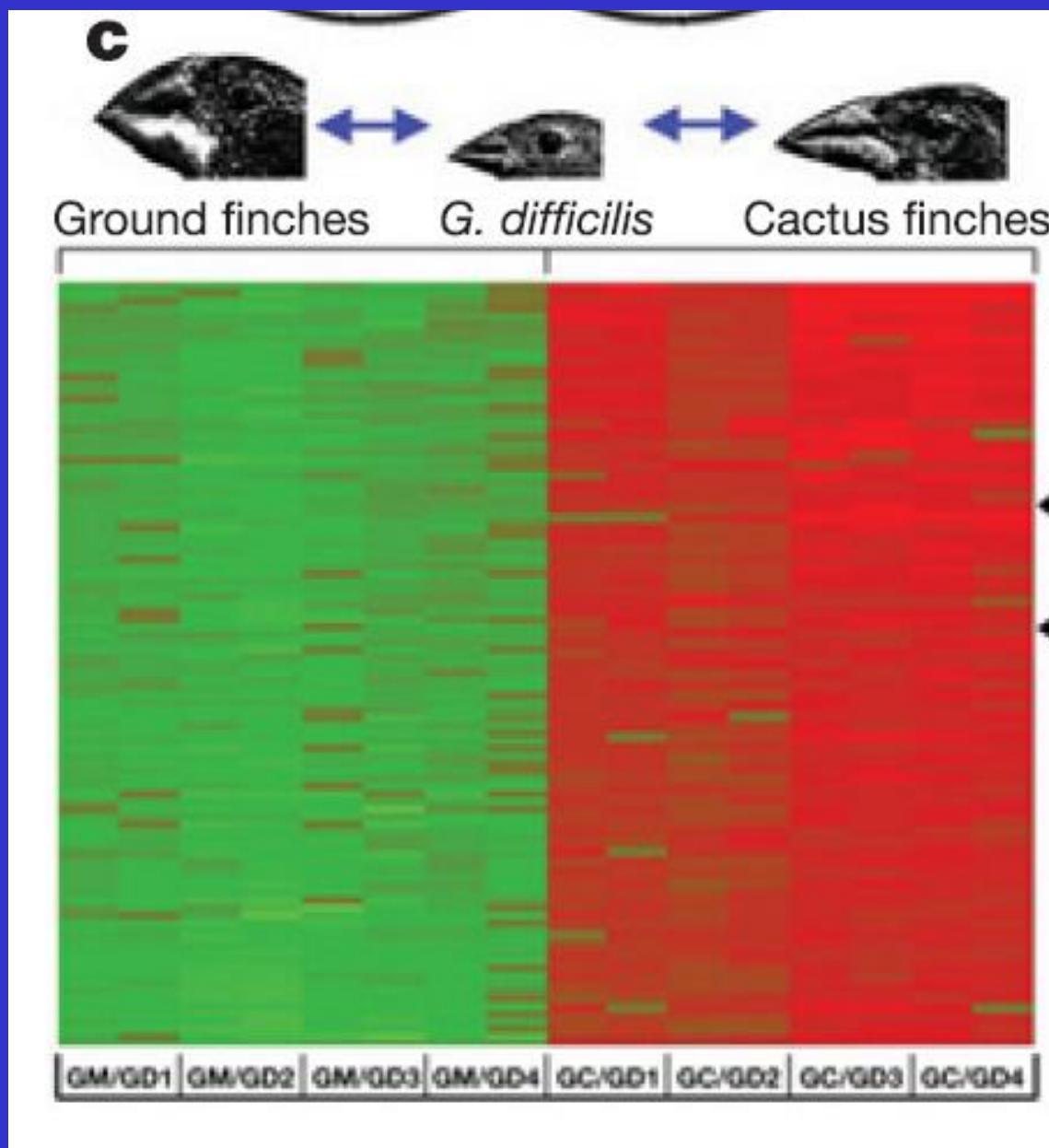
LETTERS

## The calmodulin pathway and evolution of elongated beak morphology in Darwin's finches

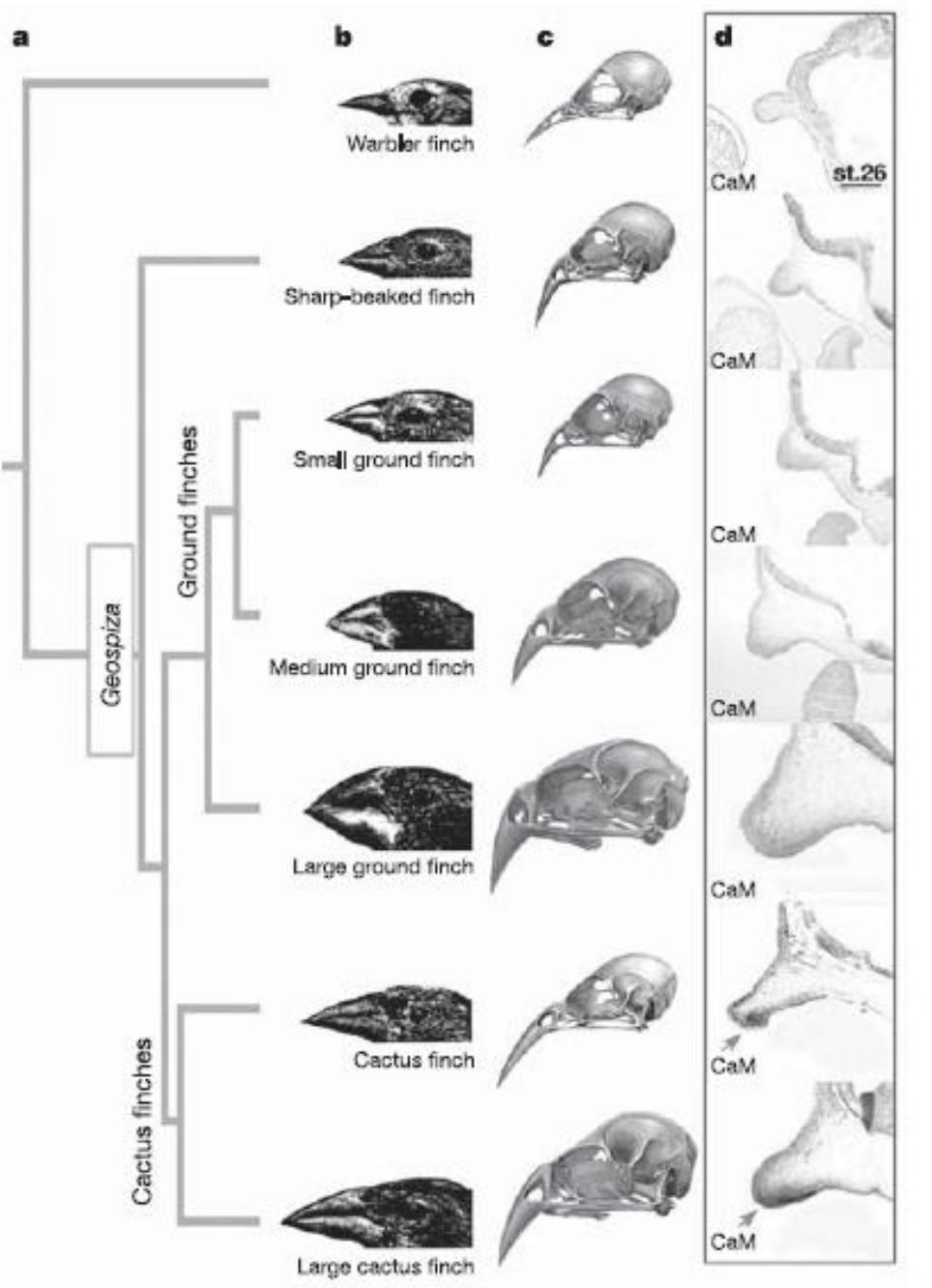
Arhat Abzhanov<sup>1</sup>†, Winston P. Kuo<sup>1,2,3</sup>†, Christine Hartmann<sup>4</sup>, B. Rosemary Grant<sup>5</sup>, Peter R. Grant<sup>5</sup> & Clifford J. Tabin<sup>1</sup>

# 四种典型达尔文雀的喙

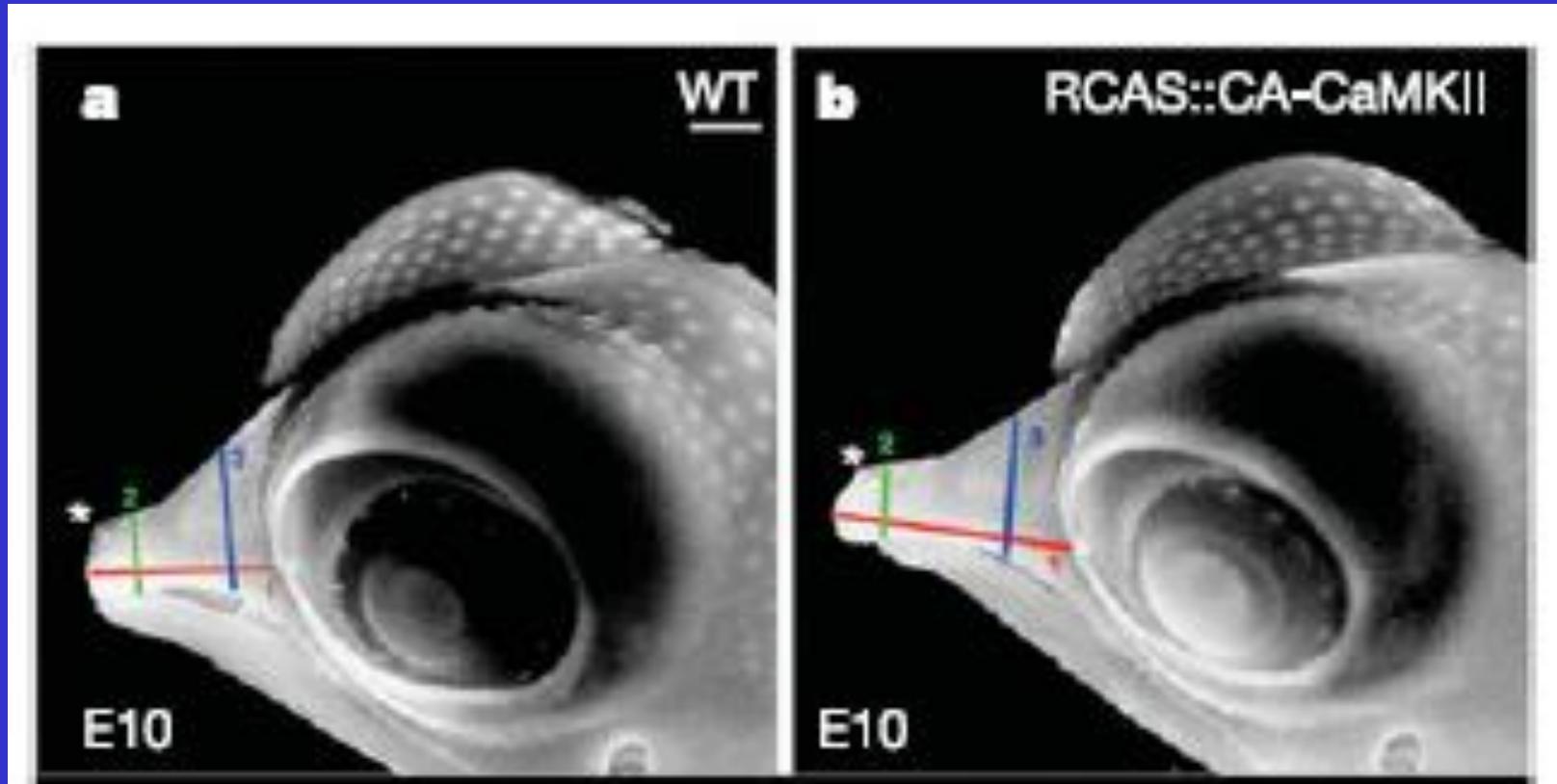




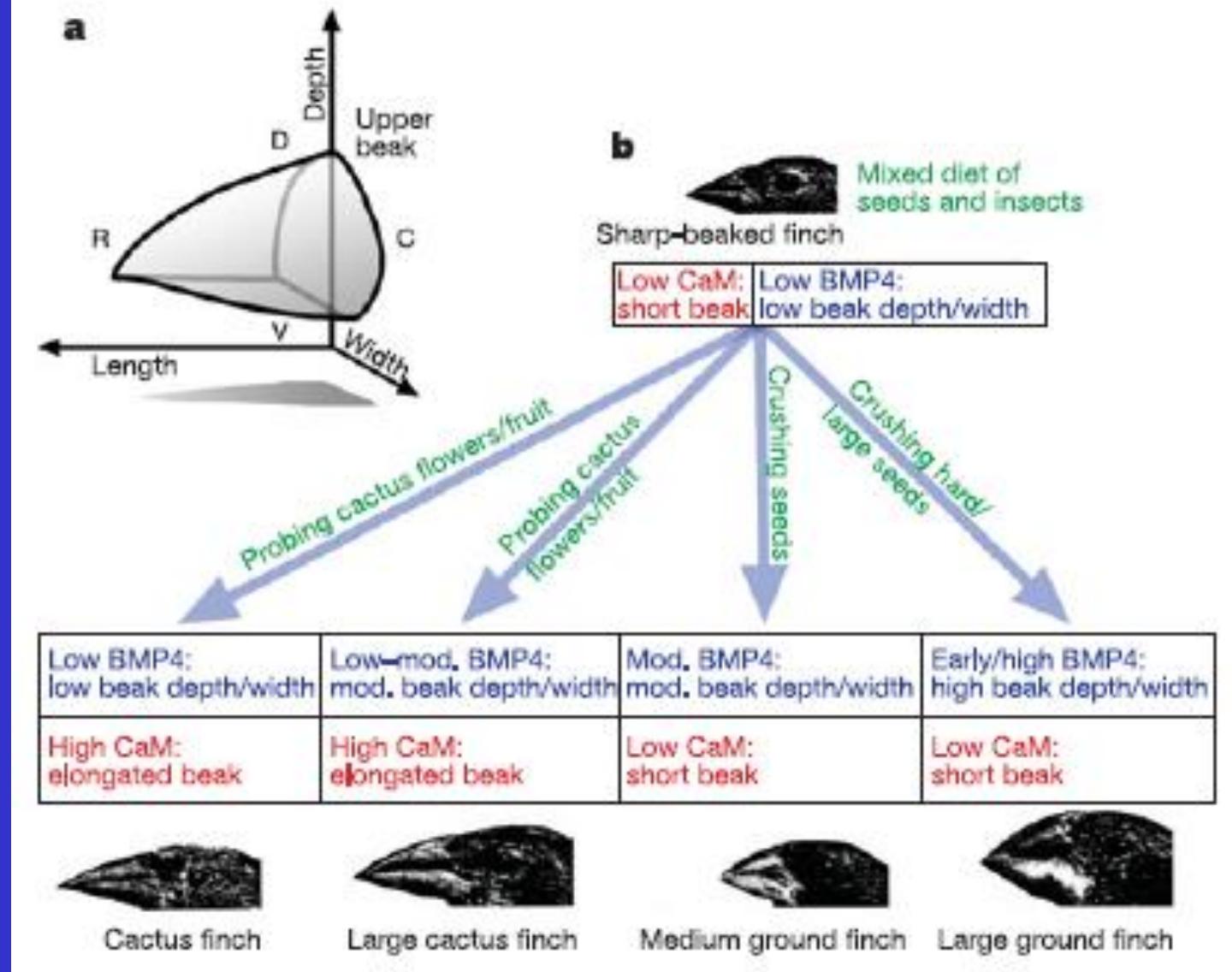
在基因表达谱中挖掘出与喙形态强烈相关的备选基因



最有可能影响喙长度的基因之一CaM  
基因在各种喙形态的达尔文雀头面部  
的表达情况



人为调高CaM基因表达量后，鸡胚胎中喙的长度果然变长

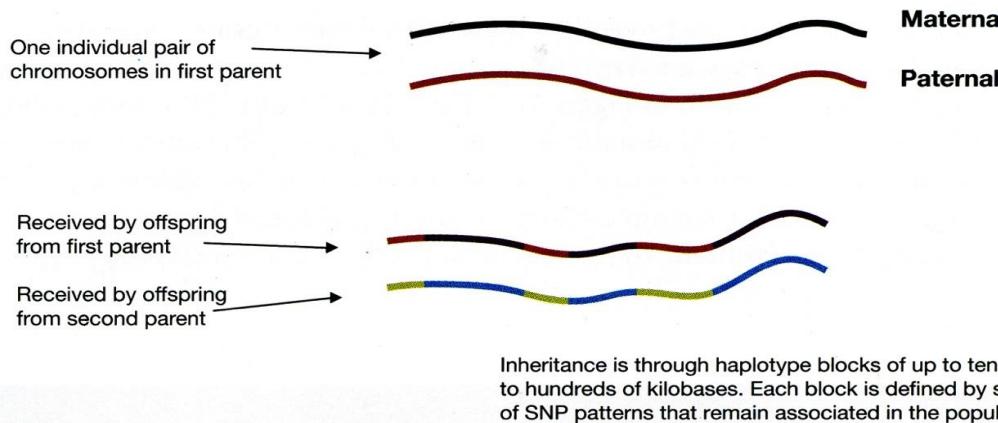


- 结合以前对BMP4基因的研究，得出达尔文雀喙形态发育的基因调控模型
- BMP4 上调，则喙变宽变深，CaM上调，则喙变长

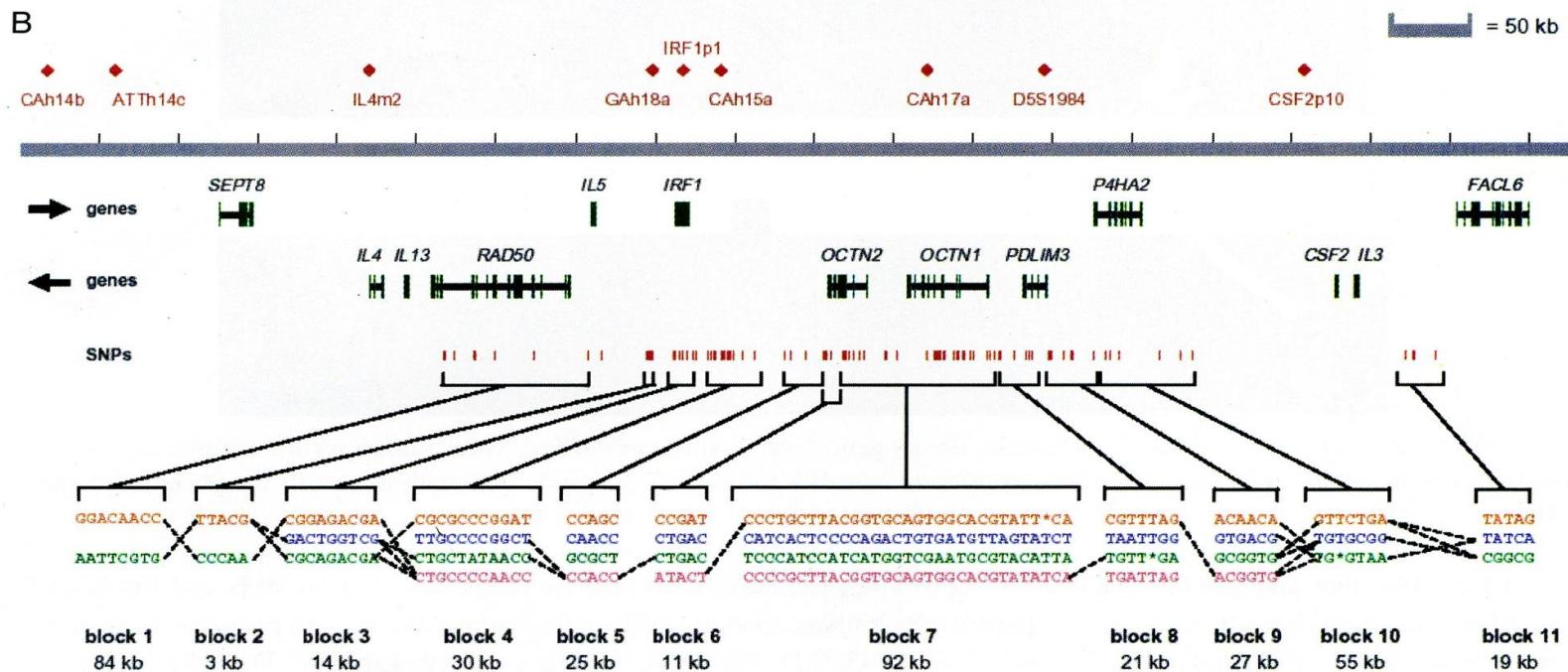
# SNP and Haplotype

A

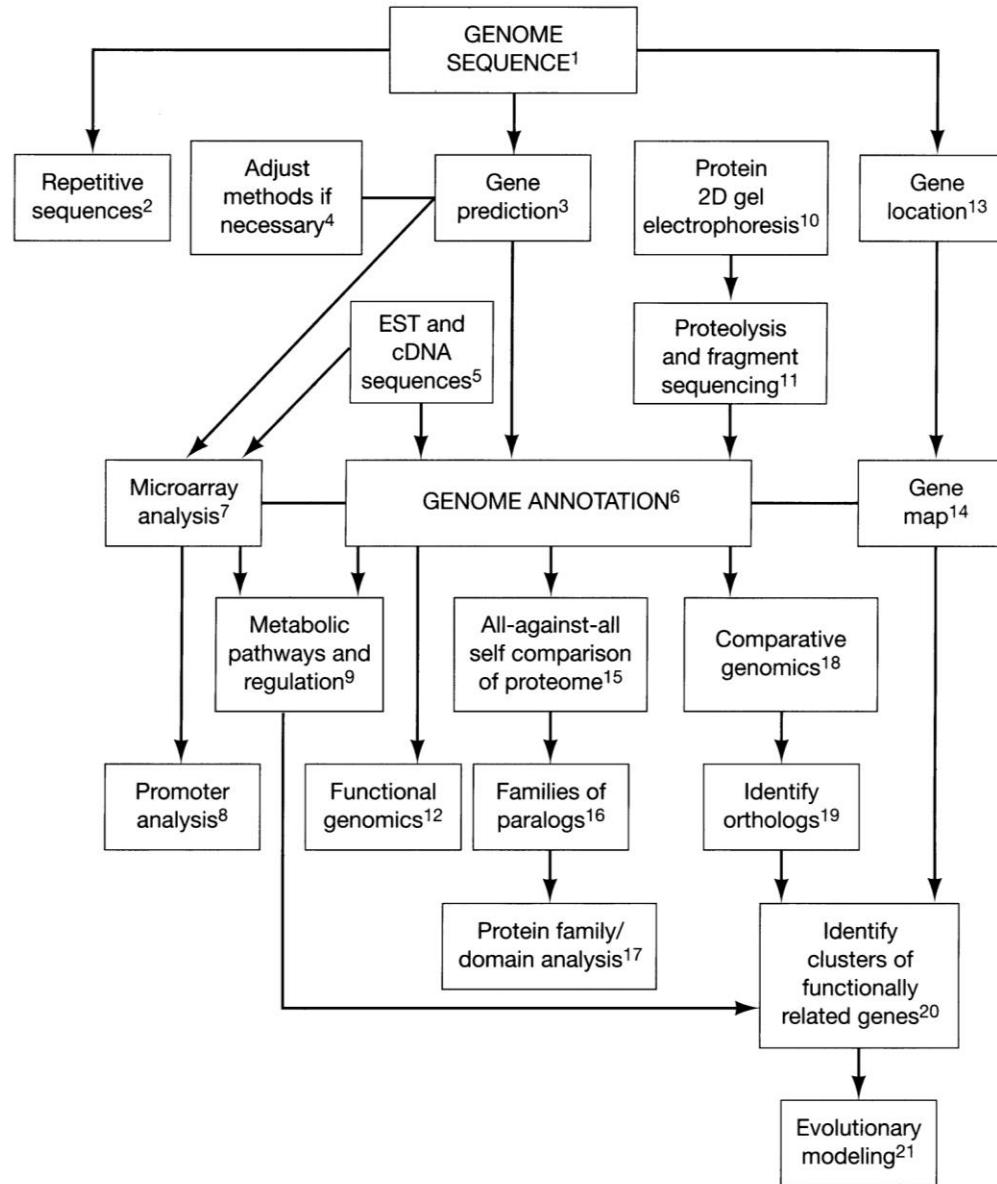
Chromosomes differ by hundreds of thousands of differences in sequence called SNPs (single nucleotide polymorphisms).

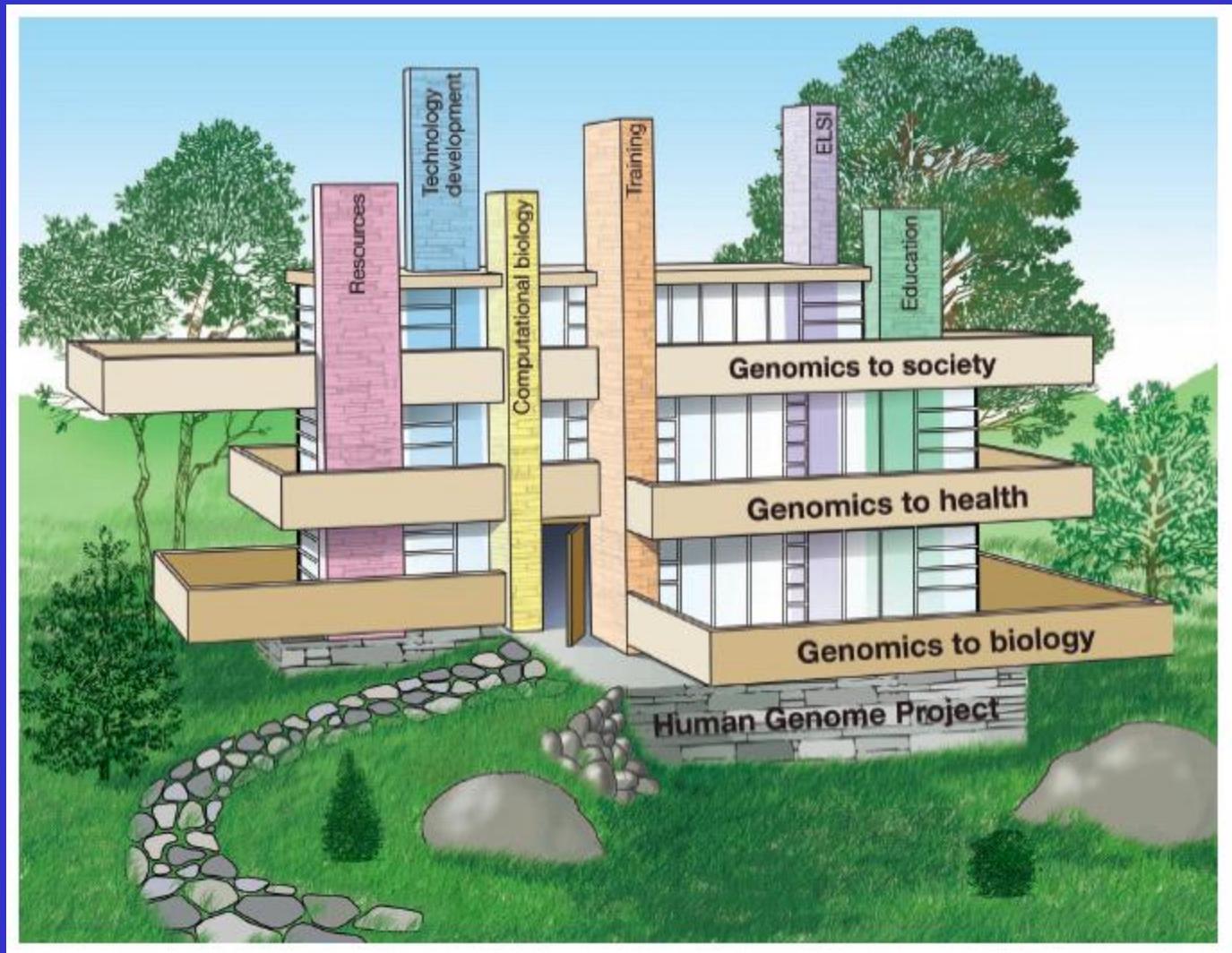


B



# Genomics Analysis

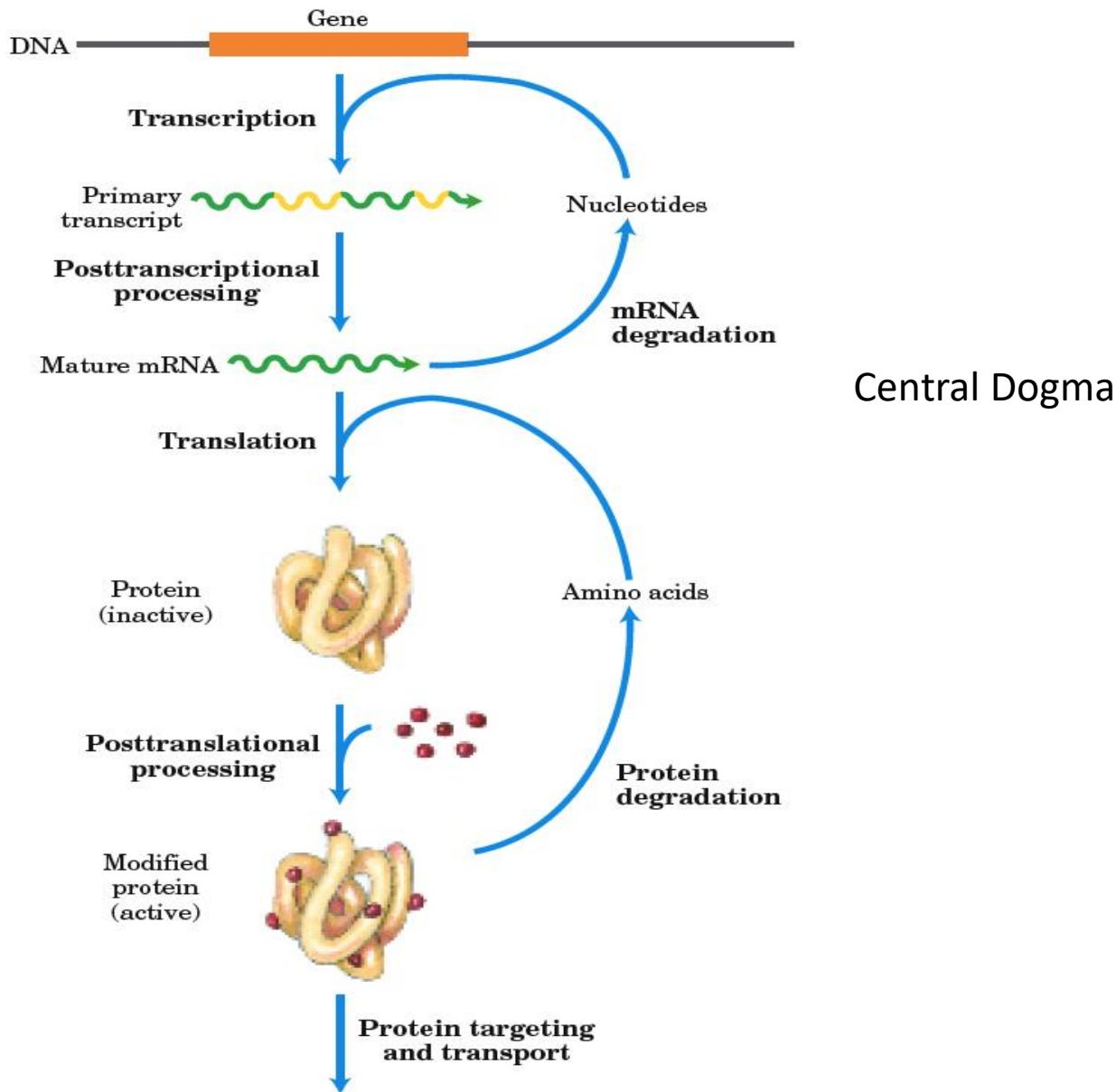




*Francis S. C. Nature. 2003, 422:835-847*

# Gene Regulatory Network

# Genes





François Jacob

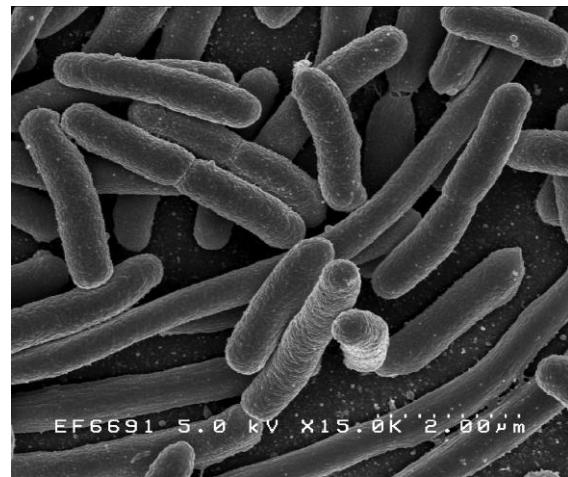
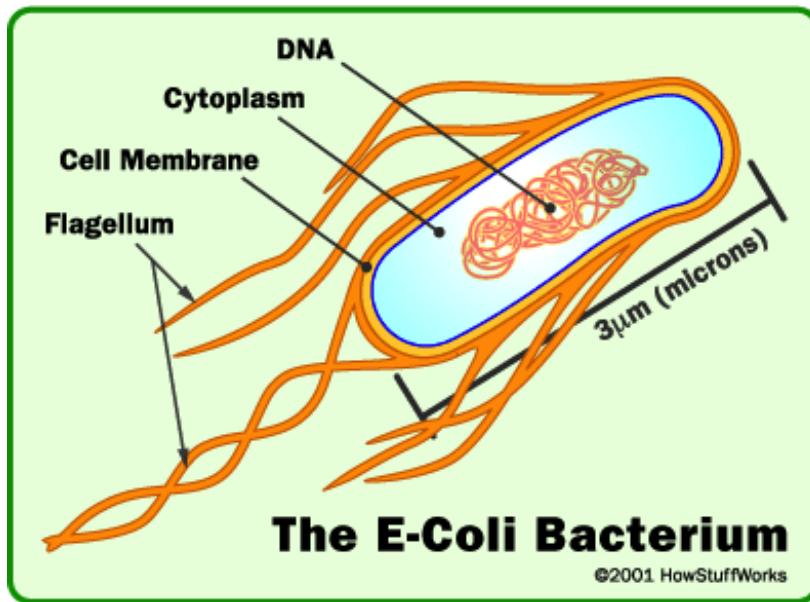


Jacques Monod, 1910–1976

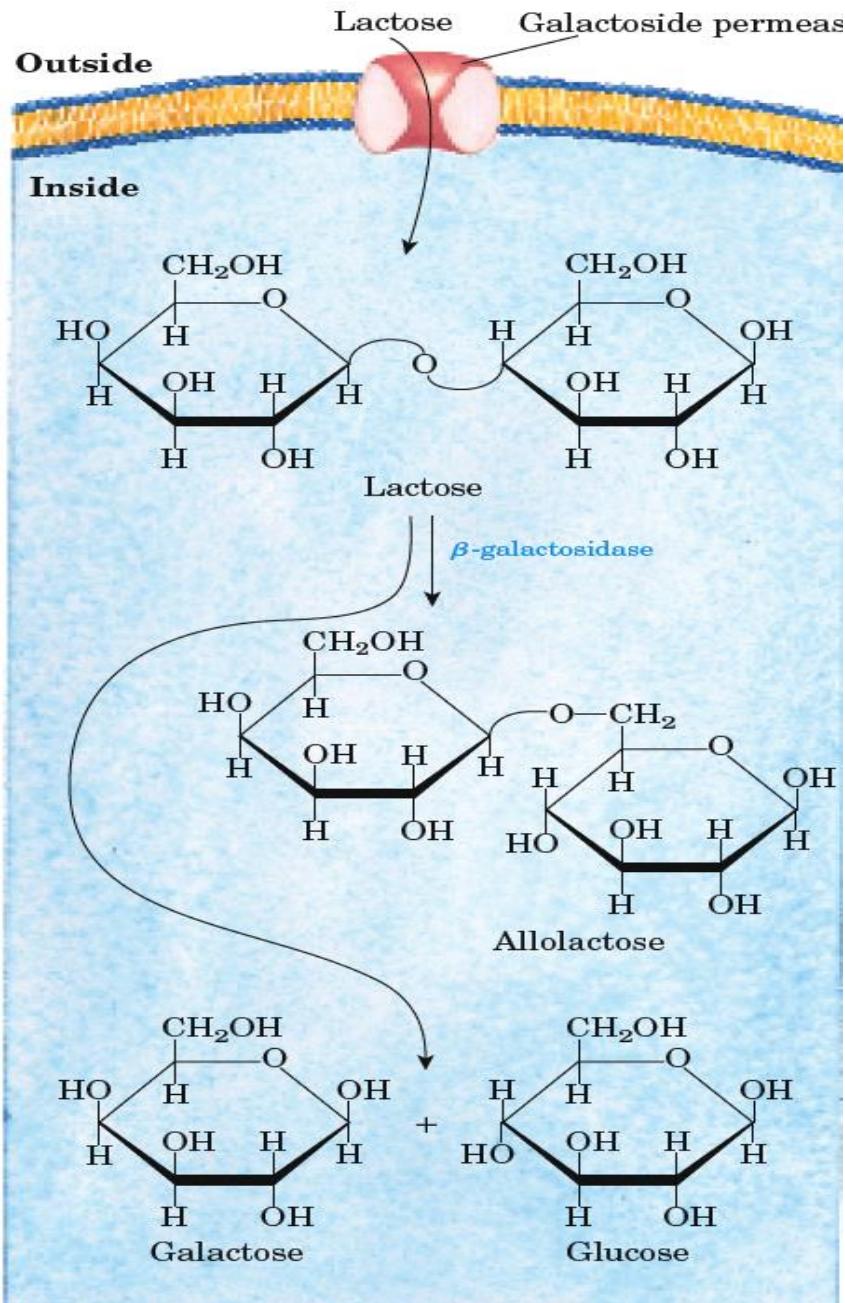
The fundamental problem of chemical physiology and of embryology is to understand why tissue cells do not all express, all the time, all the potentialities inherent in their genome.

*—François Jacob and Jacques Monod,  
article in Journal of Molecular Biology, 1961*

# E. Coli

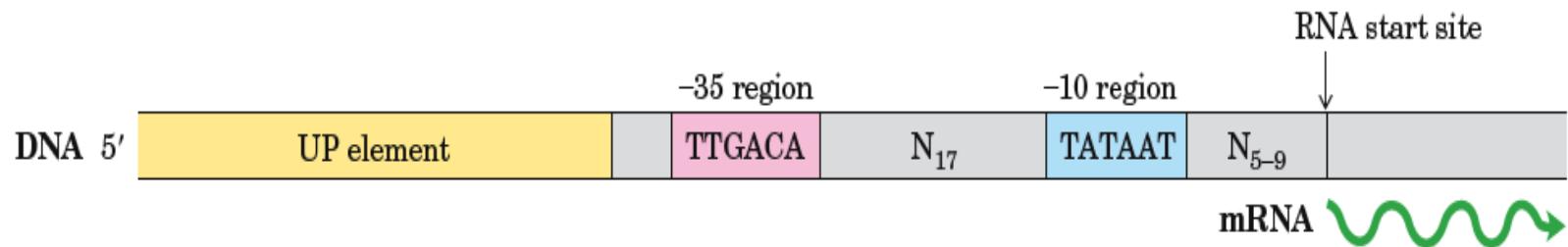


Biologist's equivalent of Hydrogen atom.



## Lactose Metabolism In *E. Coli*

# Promoter

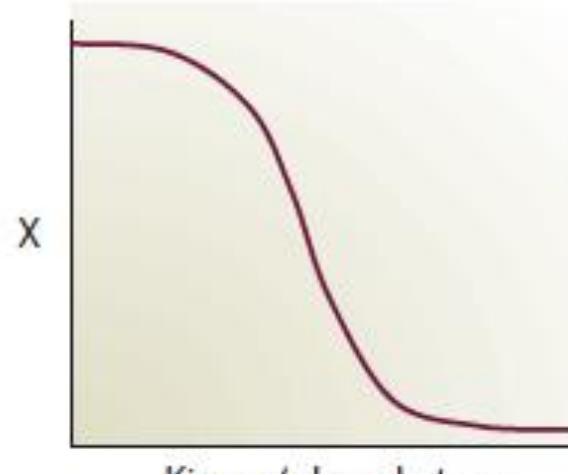
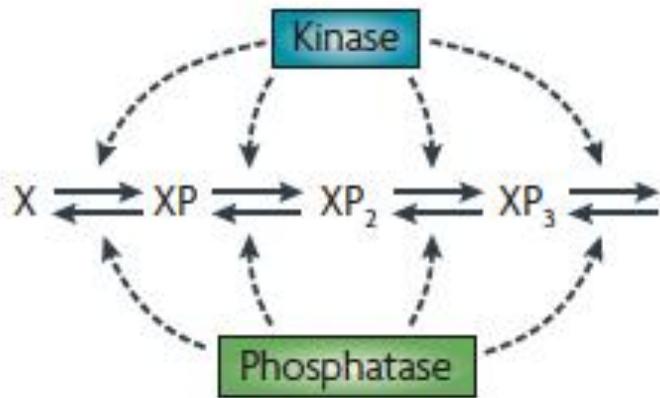




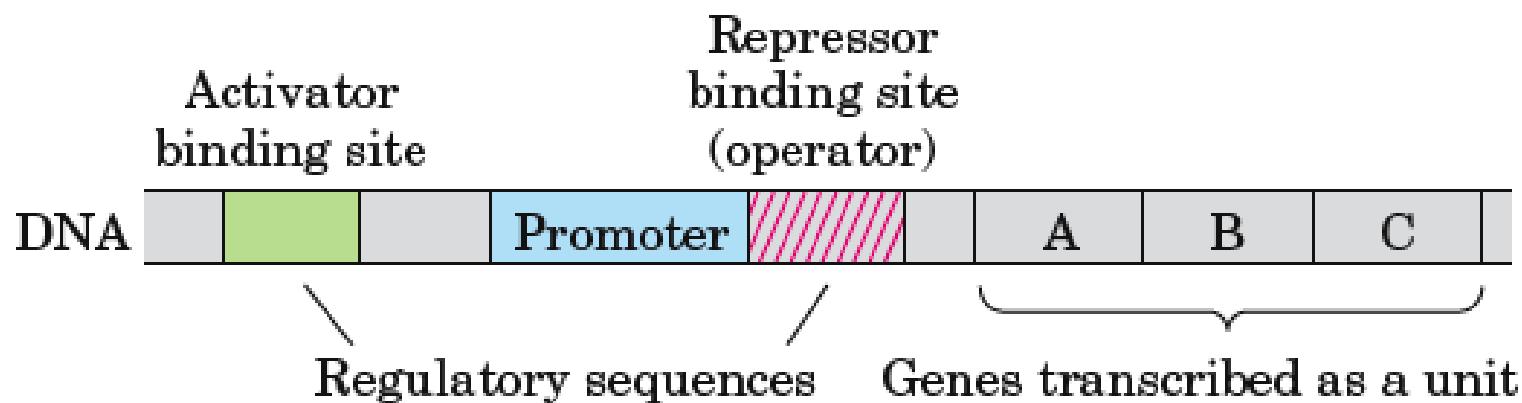
INSTITUTE OF NEUROSCIENCE

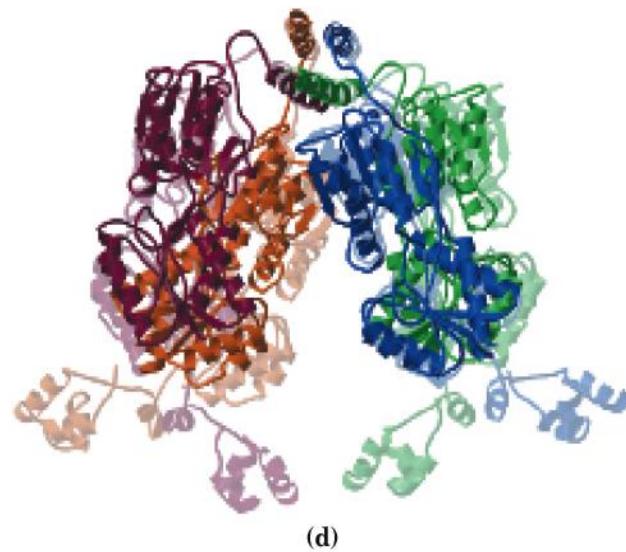
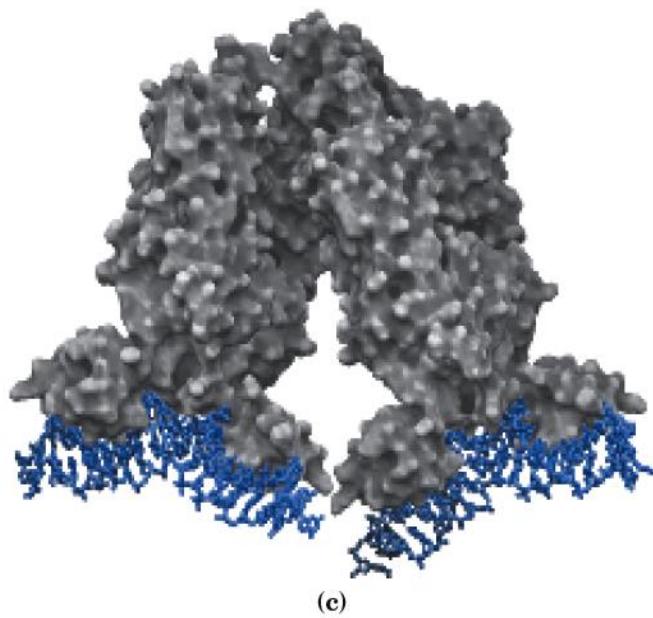
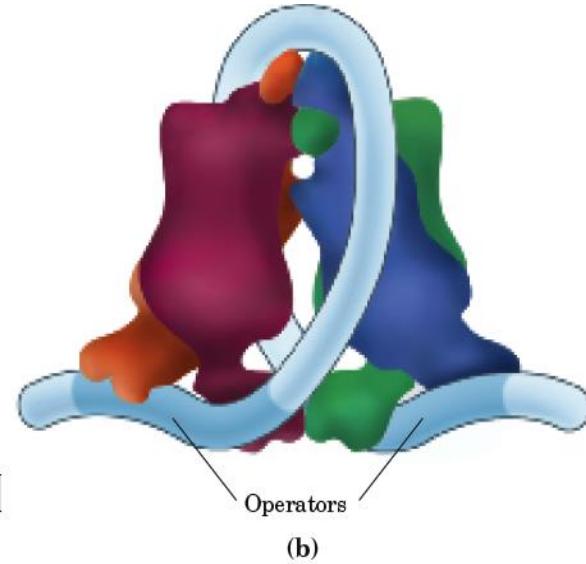
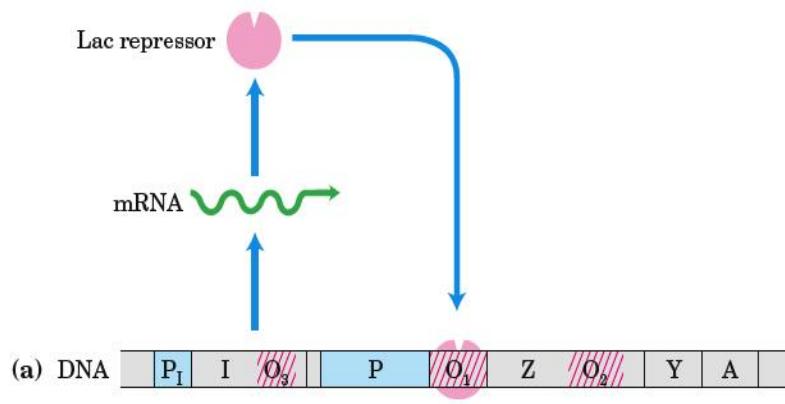
中国科学院神经科学研究所

## 基因调控



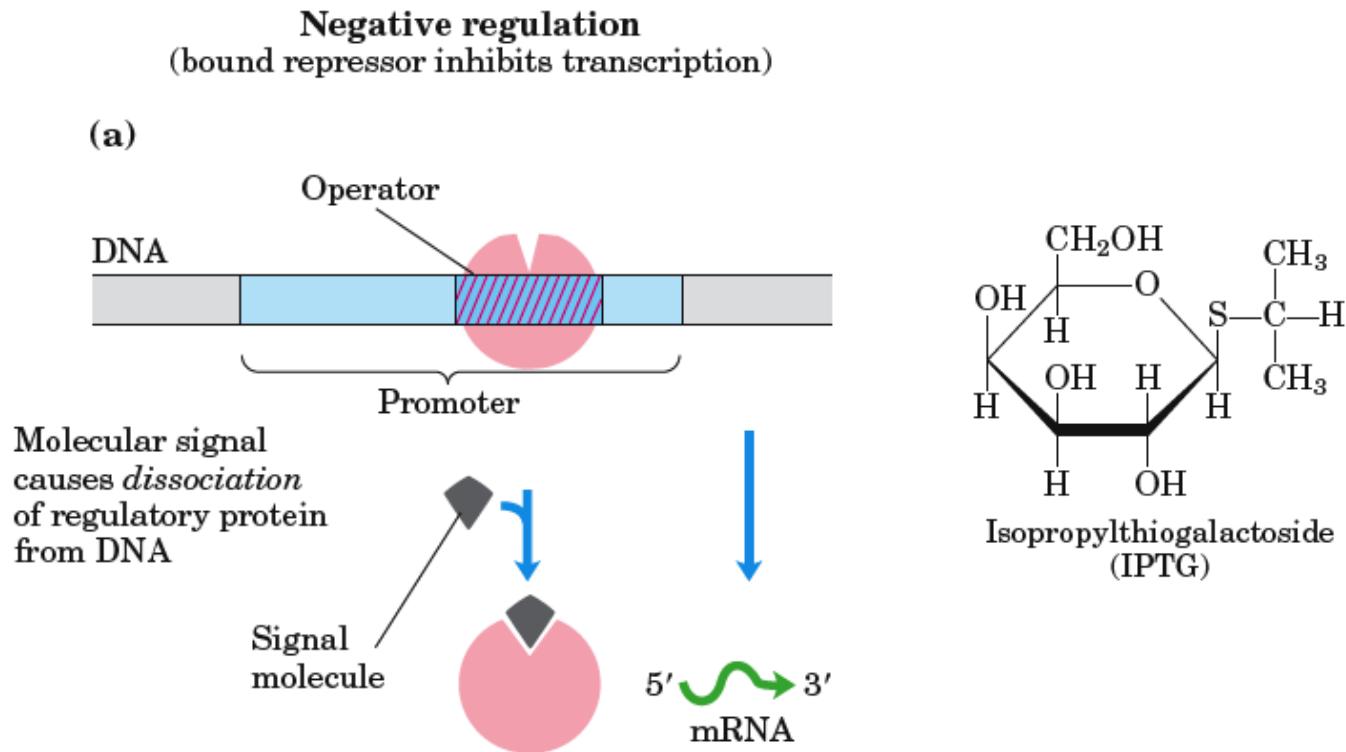
# Operon



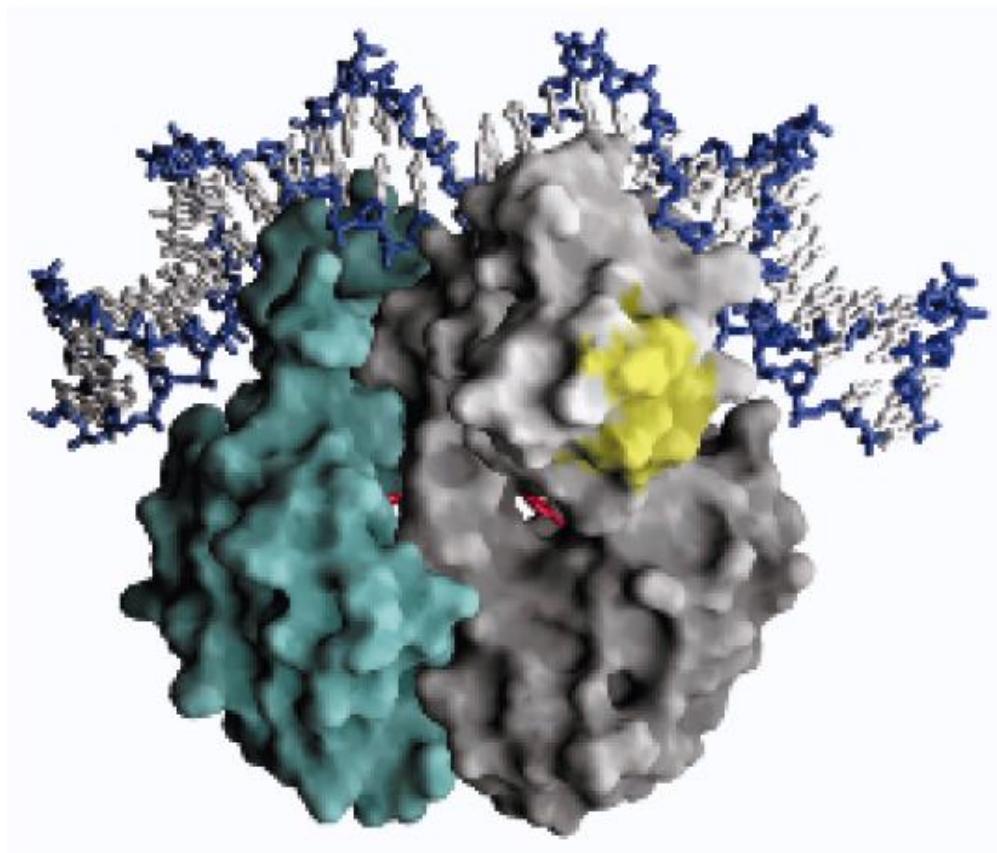


Lac I Repressor

# Substrates can relieve Lac I repression



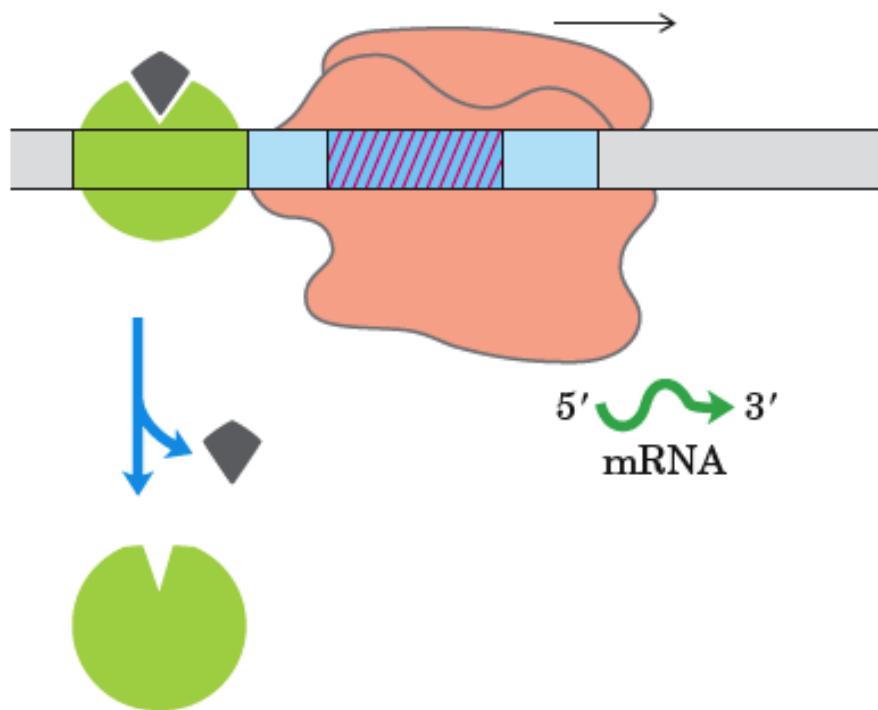
# Positive regulator: CRP

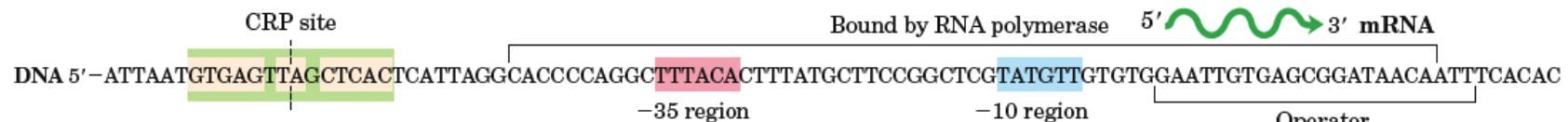


CRP: cAMP receptor protein

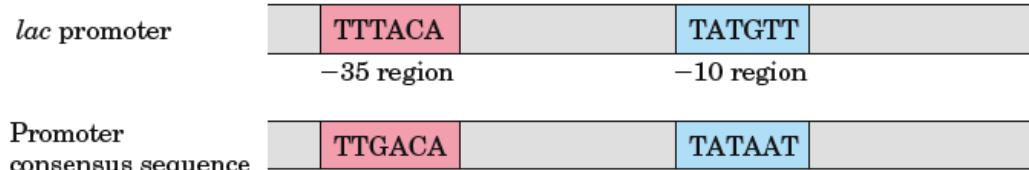
cAMP activates CRP

(d)

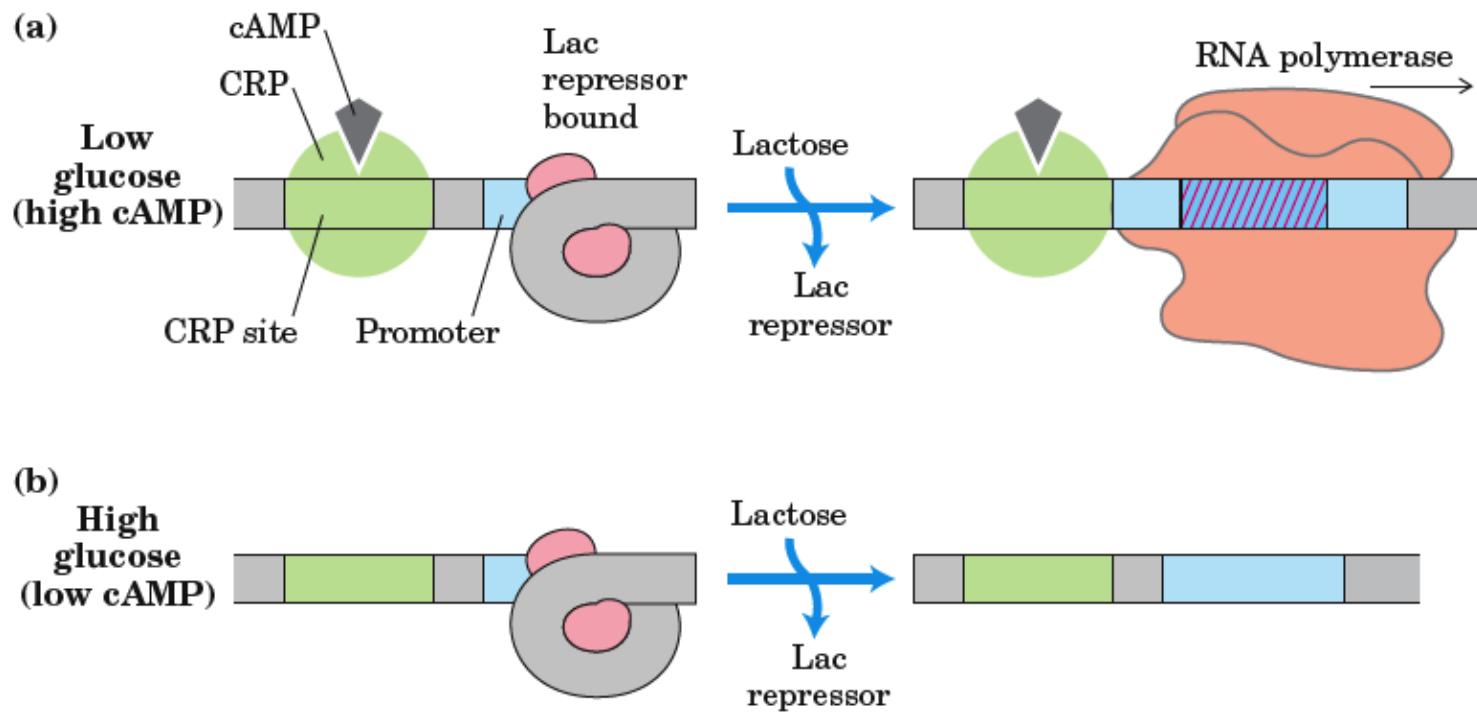




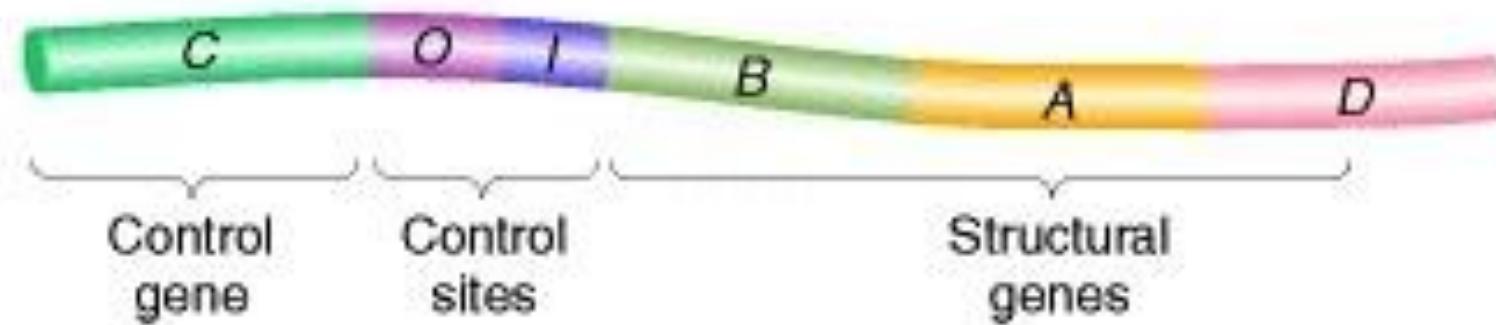
(a)



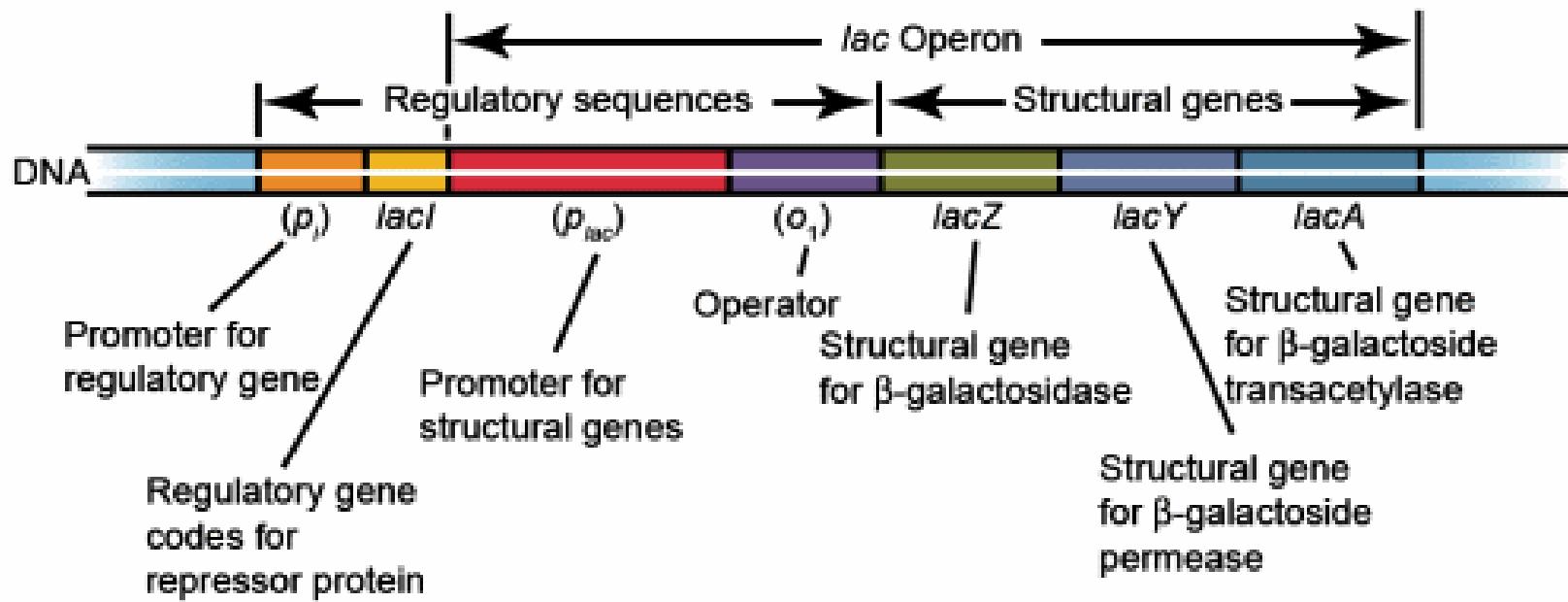
(b)



# E. Coli operon structure

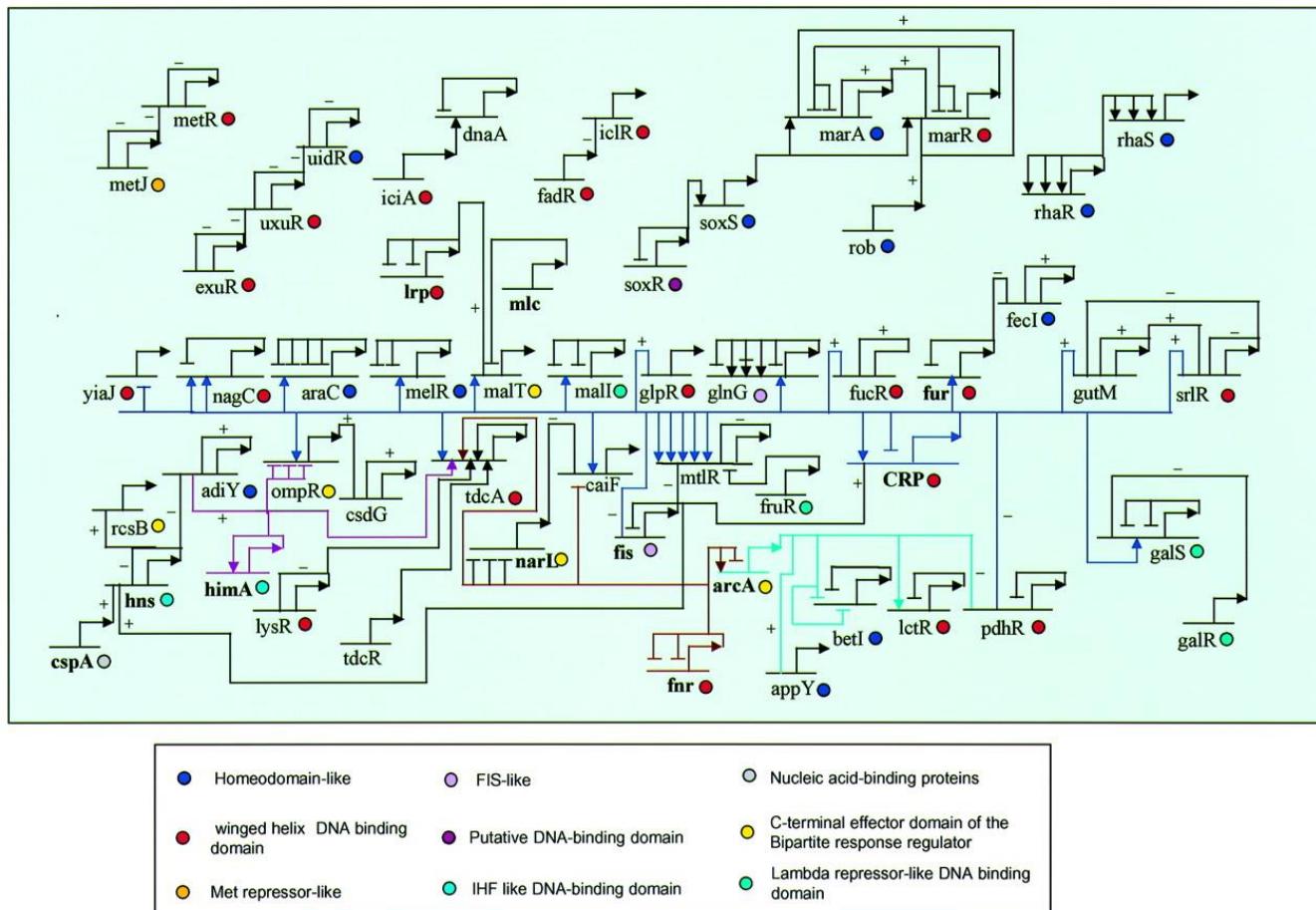


# Lac operon



# Gene Regulatory Networks

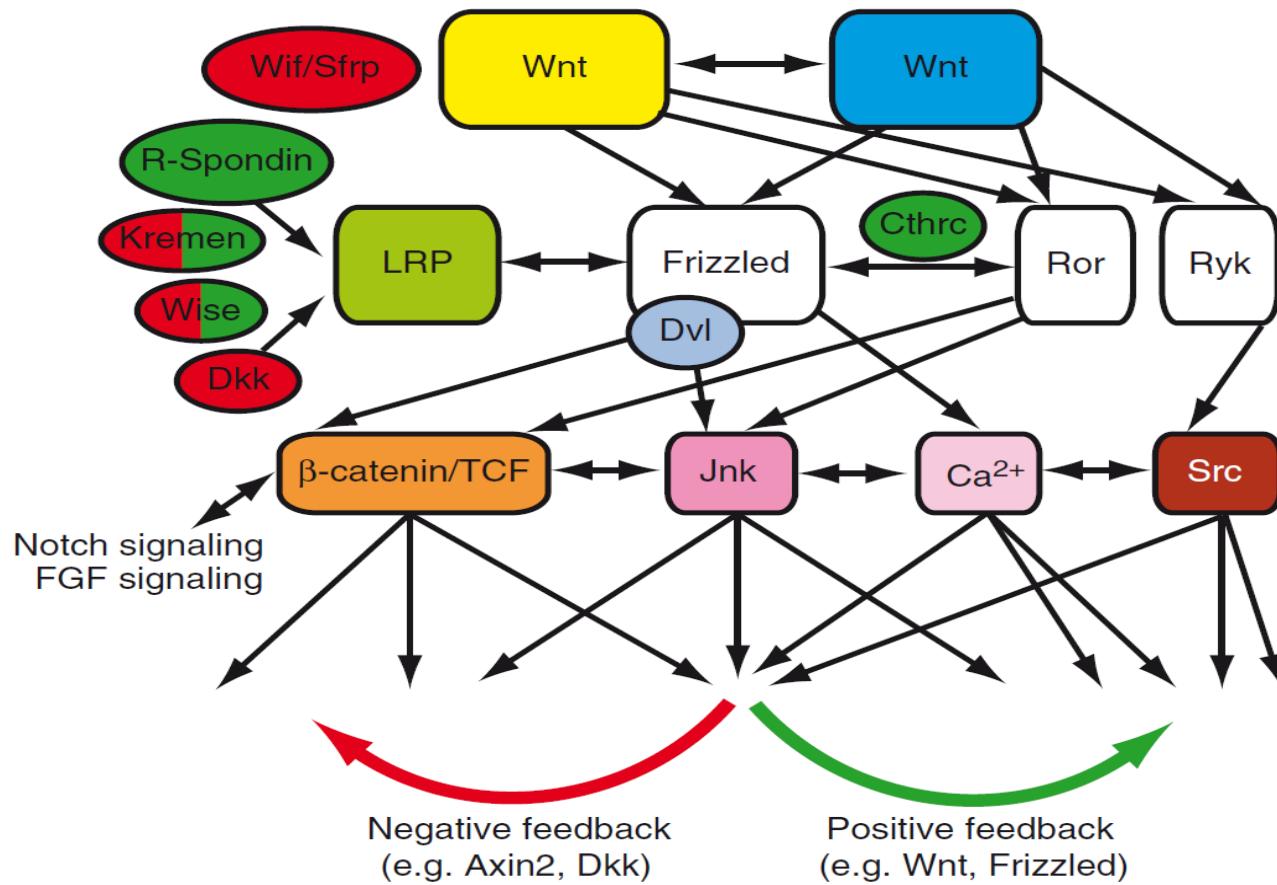
## *Regulation of transcription factors in E. coli*



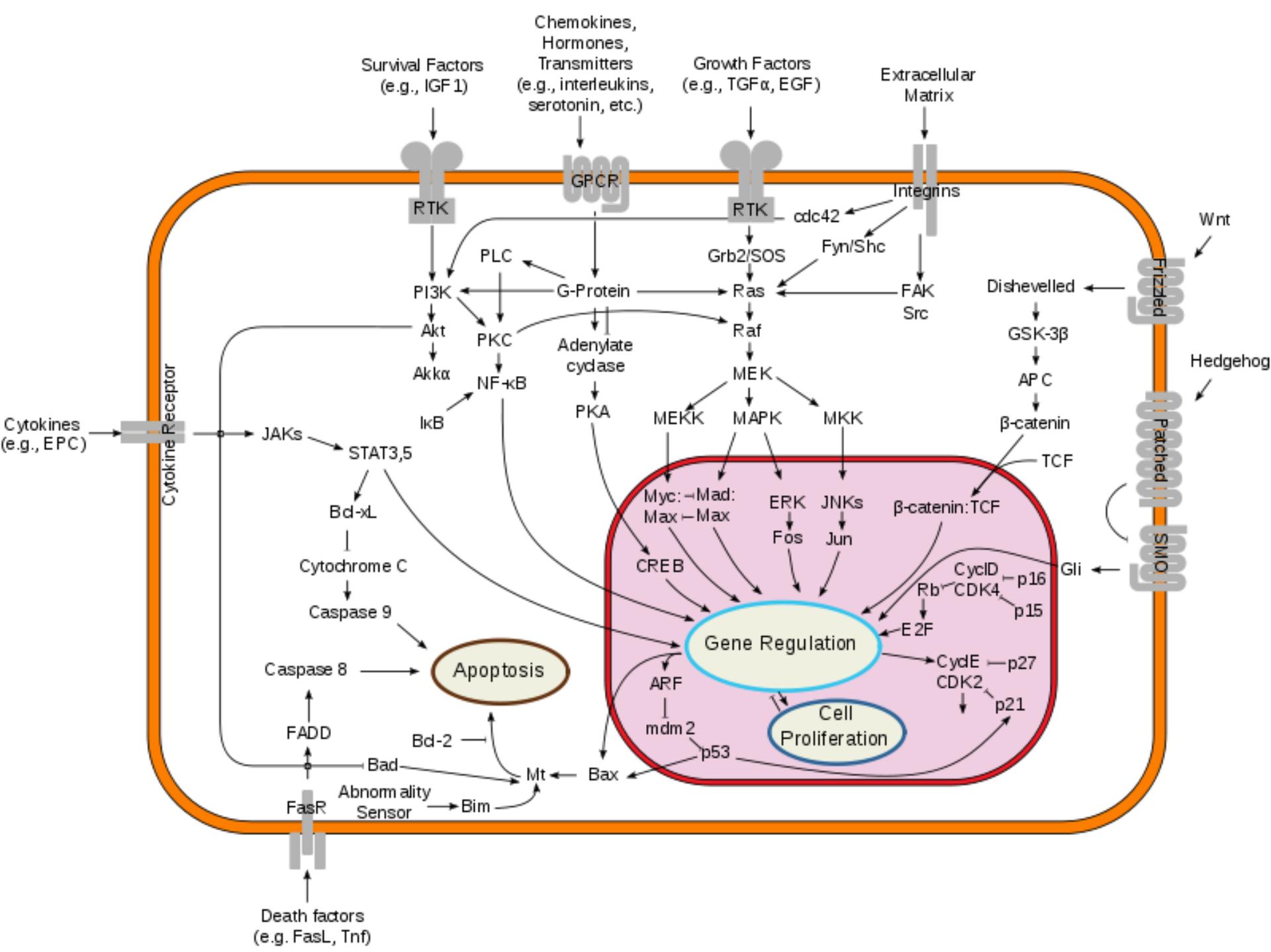
Babu et al. Nucl. Acids Res. (2003) 31 (4): 1234-1244.

# Signal Transduction Networks

Representation of a signal transduction network based on more detailed experimental evidence



van Amerongen and Nusse, 2009



# The modeling of gene regulation

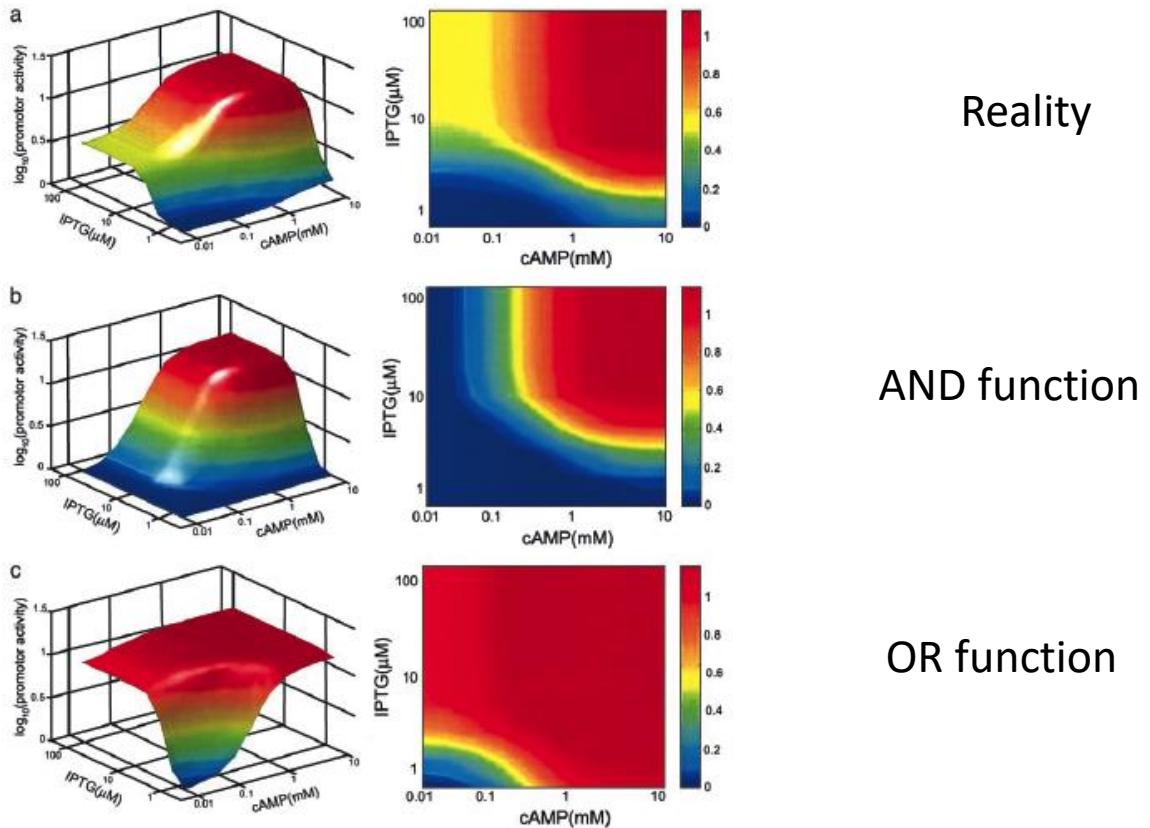
# Input function

- How to model transcription factor regulate a gene?
- Activator (Hill function)
- Repressor (anti-Hill function)
- Logic function (Activation threshold)

# Multiple Input function

- AND function
- OR function

# Multiple input function for Lac operon

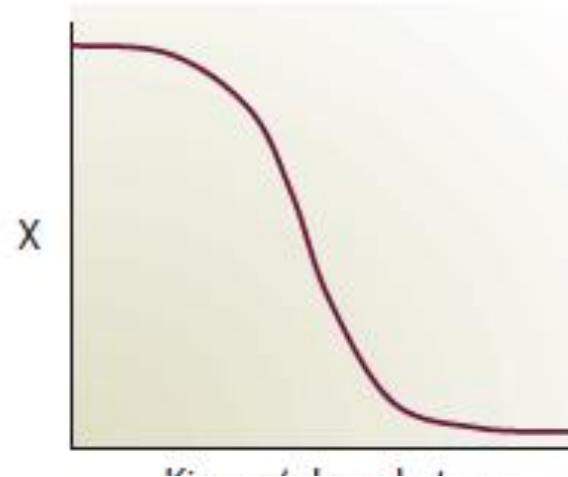
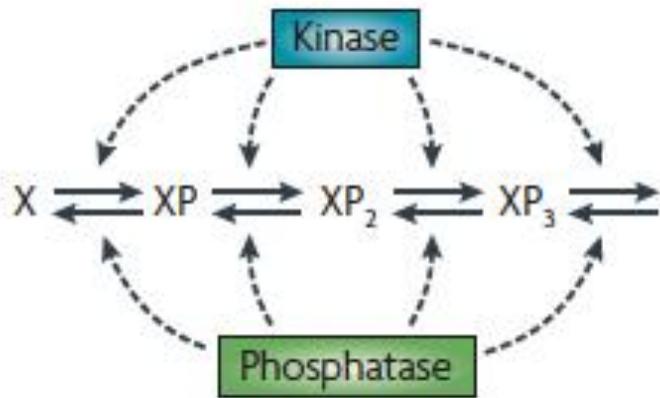




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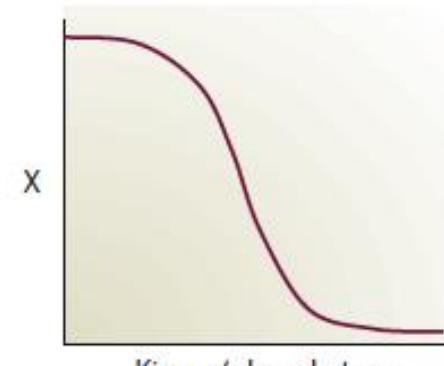
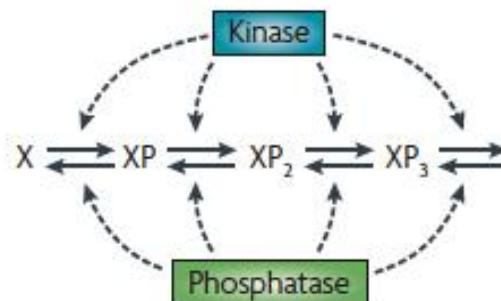
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### 基因调控



# Models for simple regulation

- Simple regulation leads to exponential relaxation to steady state.
- Response time depends on degradation or dilution time.
- Transcription factor has to cross a threshold.

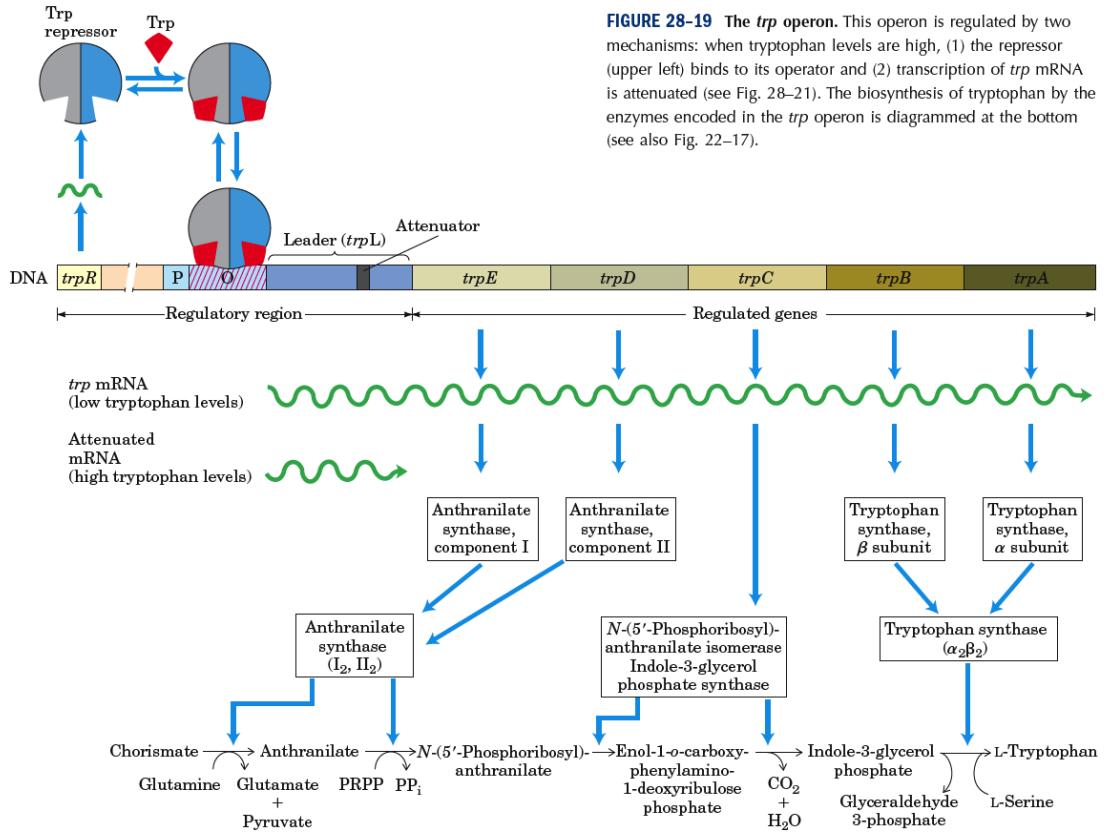


# Auto-negative regulation

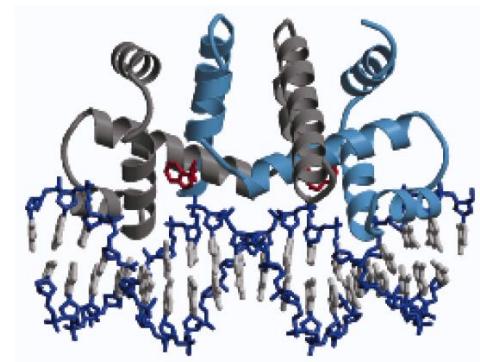
Negatively autoregulating transcription factors	Additional transcription regulation	Function
AraC	Crp	Arabinose utilization
ArgR		Arginine biosynthesis
Crp		Catabolite repression, global regulator
CysB		Cysteine biosynthesis
DsdC		Regulator of D-serine dehydratase
EmrRAB		Multidrug resistance pump
ExuR		Carbon utilization
Fis		rRNA and tRNA operons and DNA replication
Fnr		Aerobic, anaerobic respiration, osmotic balance
Fur	Crp	Iron transport
GalS	GalR	Galactose utilization
GcvA		Cleavage of glycine
GlnA	Crp, RpoN	Glutamine synthesis
Hns		Global regulator
Ihf		Integration host factor, global regulator
IlvY		Isoleucine and valine synthesis
LexA		SOS DNA repair
Lrp		Leucine response, amino acid limitation, global regulator
LysR		Lysine biosynthesis
MarA	Rob	Multiple antibiotic resistance
Mode		Molybdate transport
MtlADR		Mannitol utilization
Nac	RpoN	Histidine utilization/nitrogen assimilation
NadR		NAD biosynthesis, other roles
NagC	Crp	Repressor of genes for catabolic enzymes
OxyR		Oxidative stress
PhdR	Fis	Activator of hca cluster, other roles
PurR		Purine biosynthesis
PutAP	Nac	Proline synthesis, other roles
RpiR		Ribose catabolism
SoxS	SoxR	Superoxide stress
SrlA-D		Glucitol/sorbitol utilization
TrpR		Tryptophan biosynthesis
UxuABR	ExuR	Mannonate utilization

**Negative auto-Regulation is Wide-spread in E. coli.**

# Trp operon



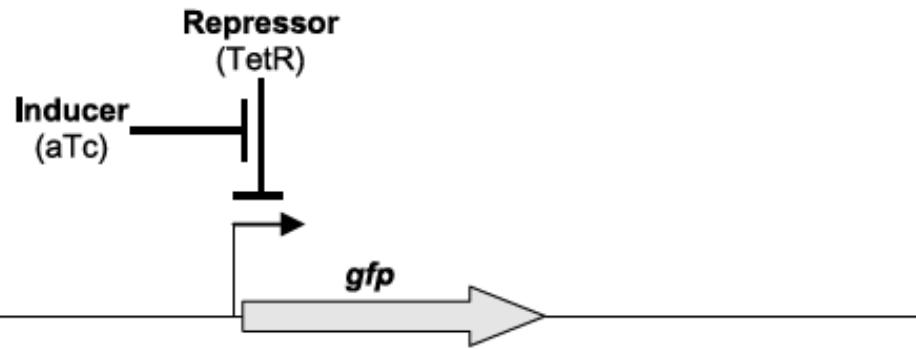
**FIGURE 28–19** The *trp* operon. This operon is regulated by two mechanisms: when tryptophan levels are high, (1) the repressor (upper left) binds to its operator and (2) transcription of *trp* mRNA is attenuated (see Fig. 28–21). The biosynthesis of tryptophan by the enzymes encoded in the *trp* operon is diagrammed at the bottom (see also Fig. 22–17).



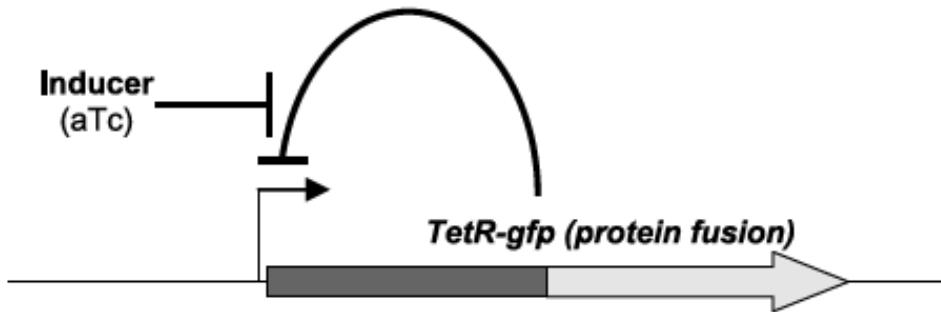
TrpR

# Artificially engineered negative autoregulatory loop

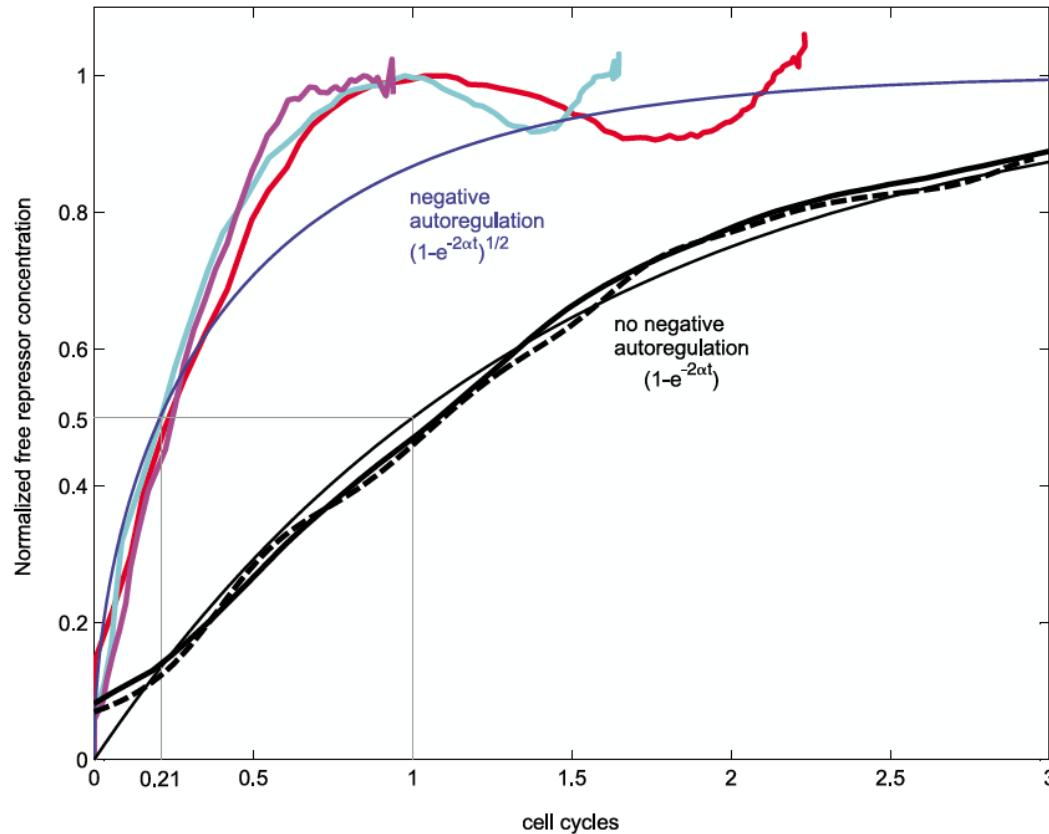
A. Simple transcription unit (open loop)



B. Negative autoregulatory circuit



# Negative auto-regulation speeds up response



# Positive auto-regulation

- Positive auto-regulation delays response.
- Act as a bi-stable switch.

# Multiple-step negative auto-regulation

- Multiple negative auto-regulation leads to oscillation.
- Stability analysis, limit cycle (Goodwin model).
- Cell cycle, metabolic cycle, circadian rhythm.

# Feed Forward Loop (FFL)

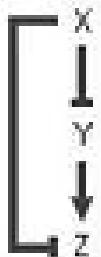
# FFL is common in gene regulatory network

## Coherent FFL

Coherent type 1



Coherent type 2



Coherent type 3

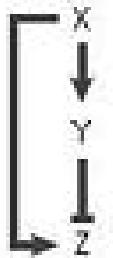


Coherent type 4

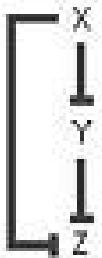


## Incoherent FFL

Incoherent type 1



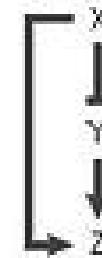
Incoherent type 2



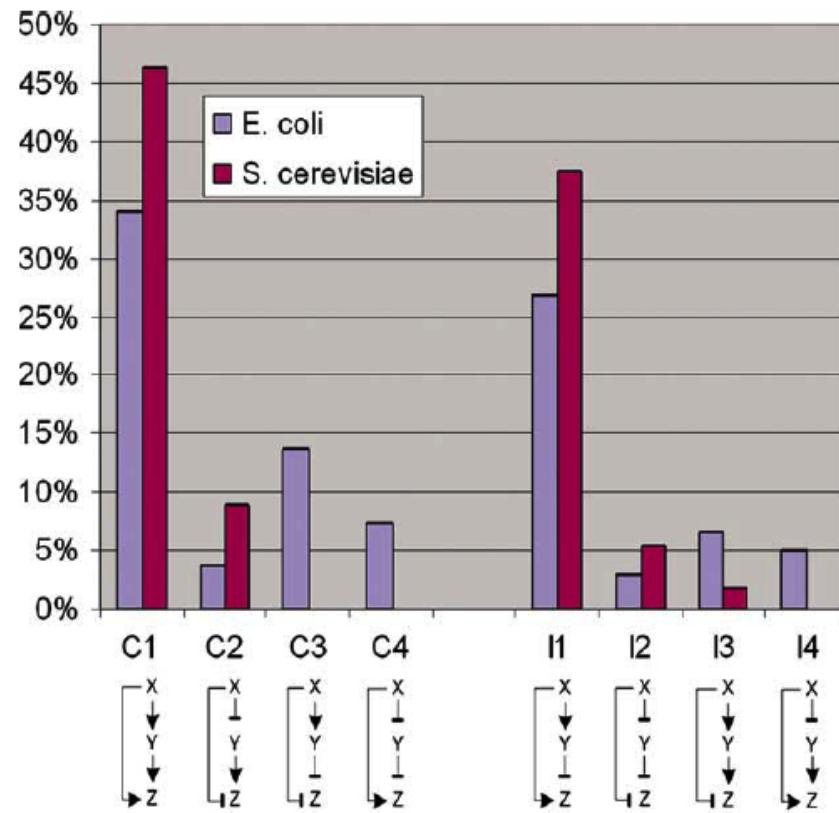
Incoherent type 3



Incoherent type 4

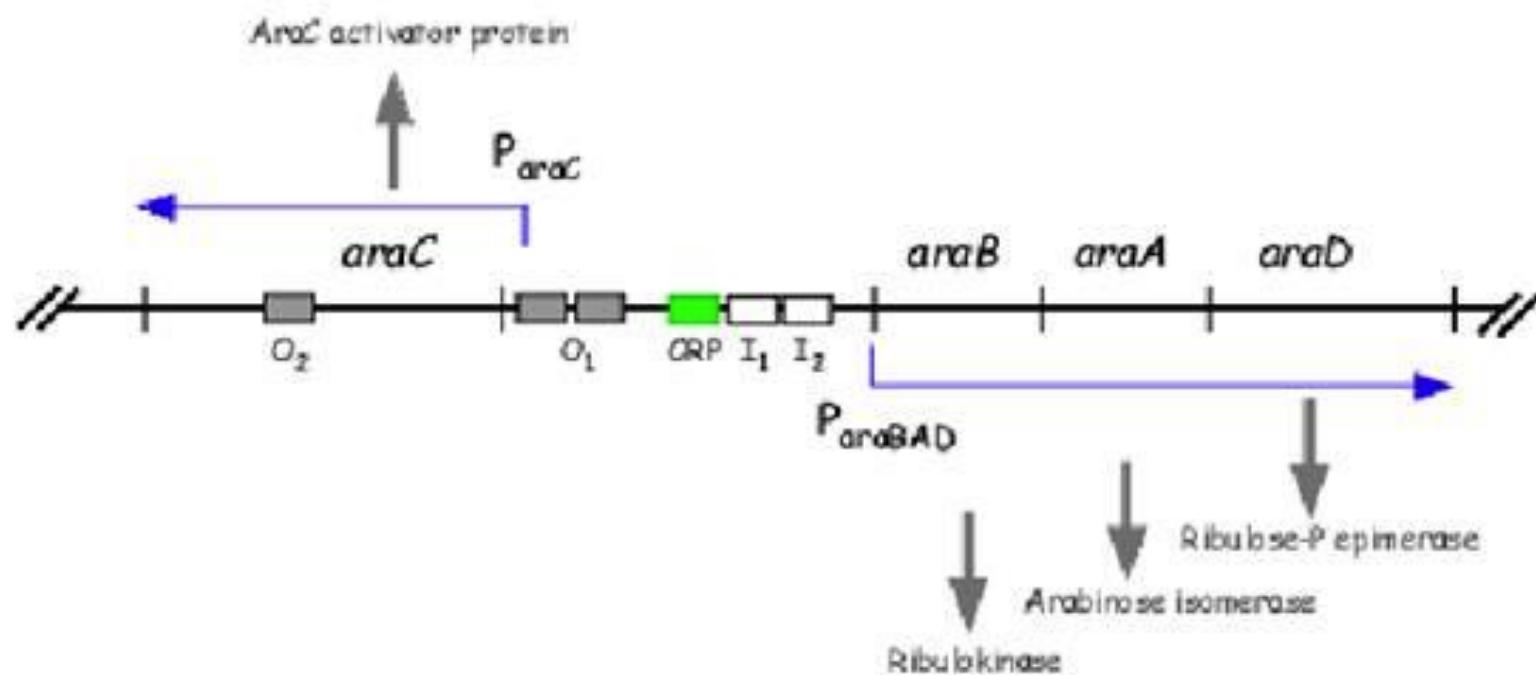


# FFL is common in gene regulatory network

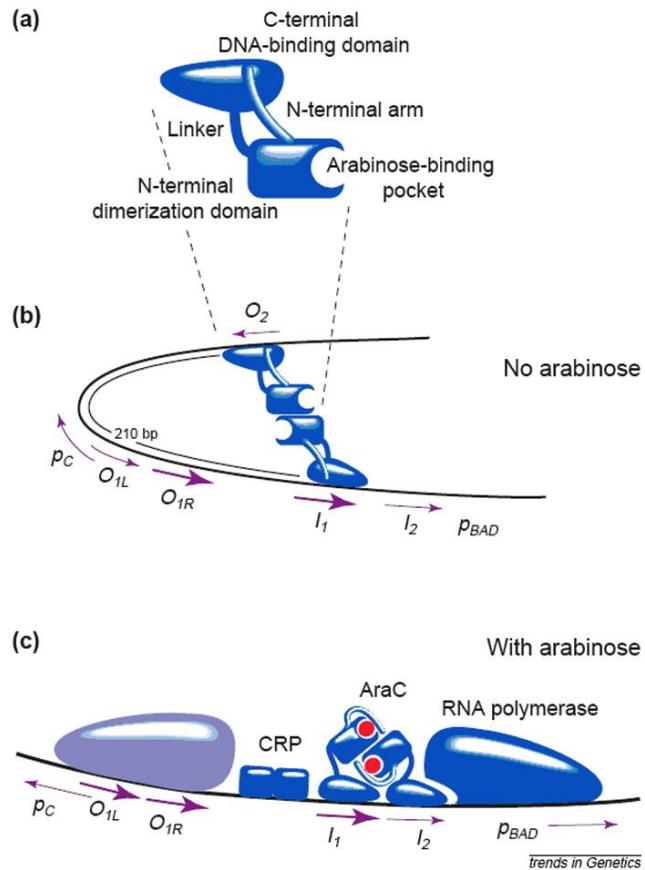


# C1 Feed Forward Loop (FFL)

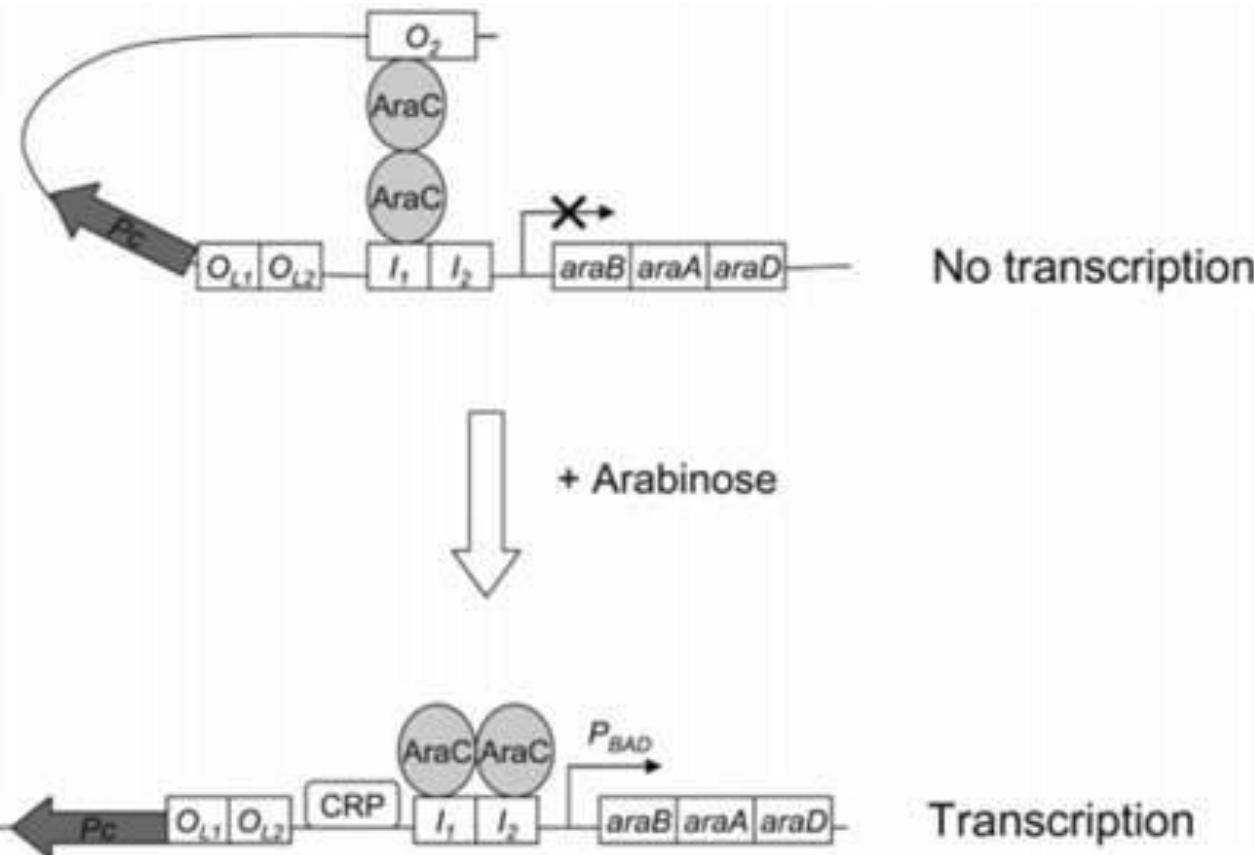
# Ara operon



# Ara operon

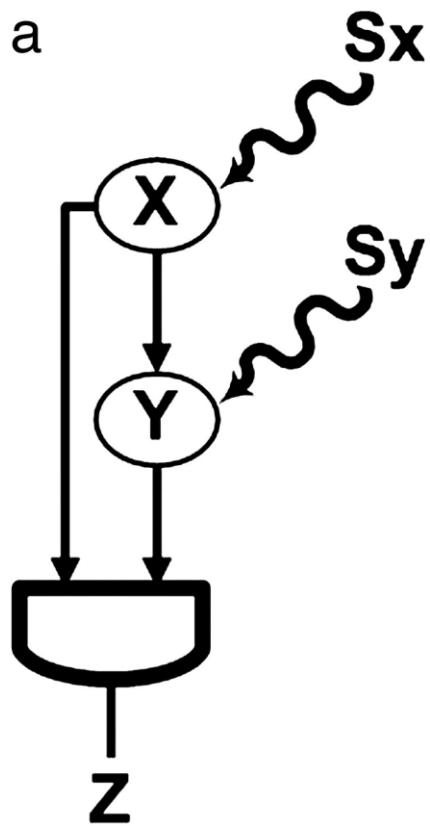


# Ara operon

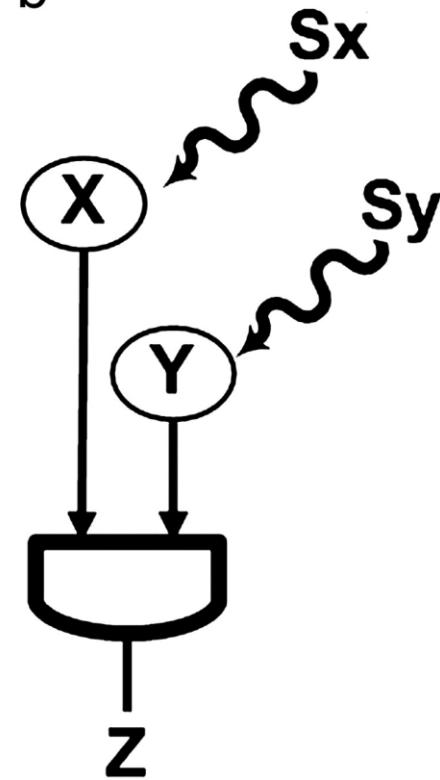


# C1 Feed-forward loop (C1FFL) vs. simple regulation

a

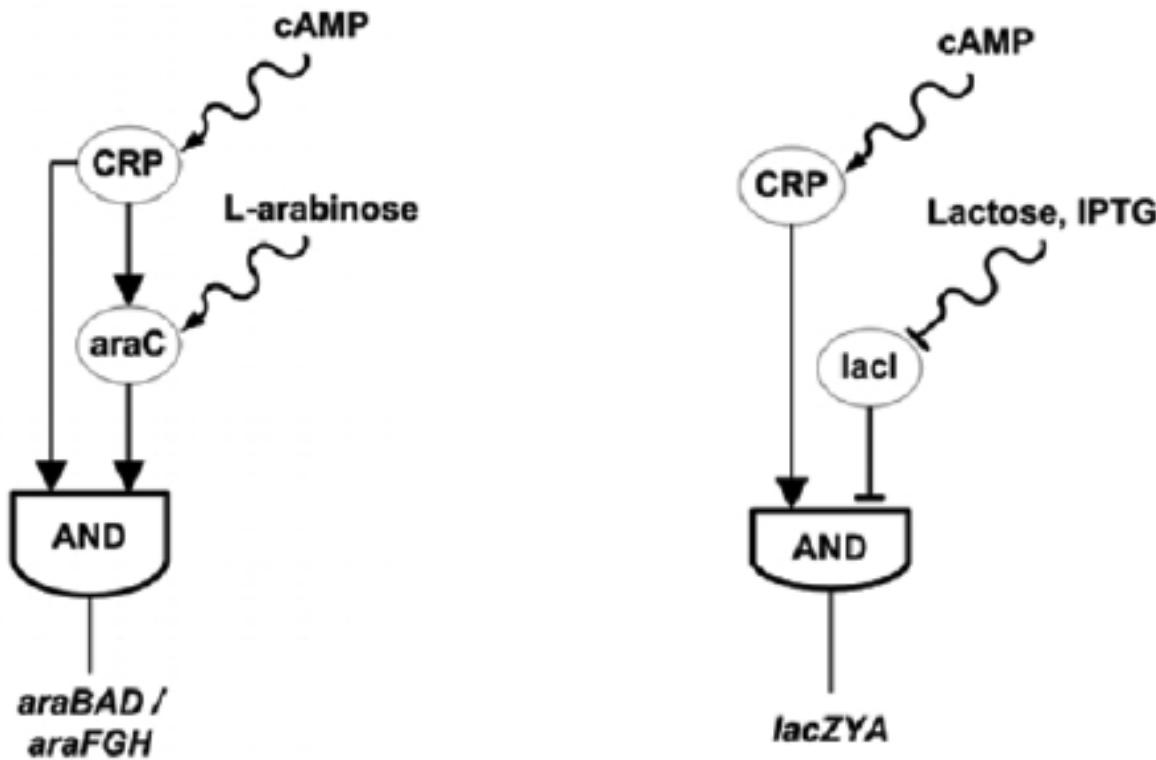


b

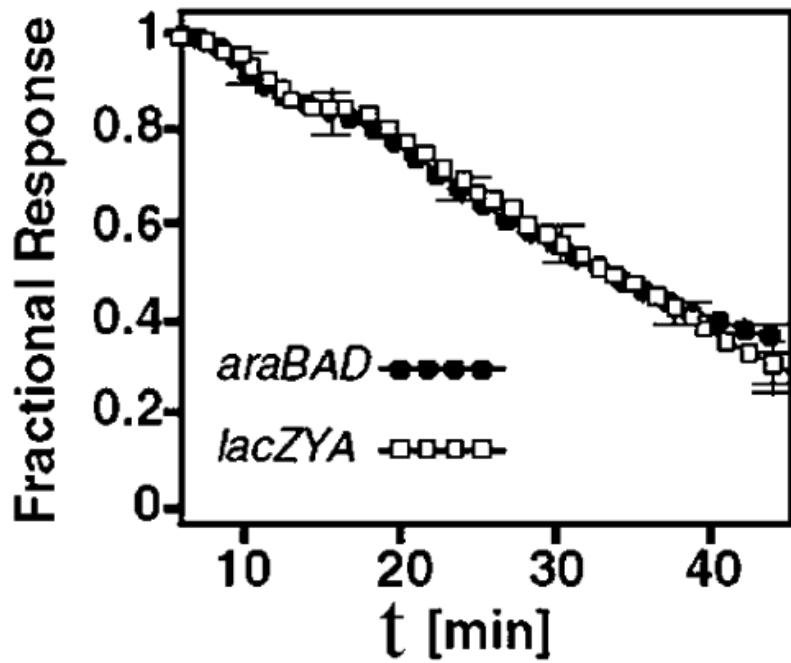
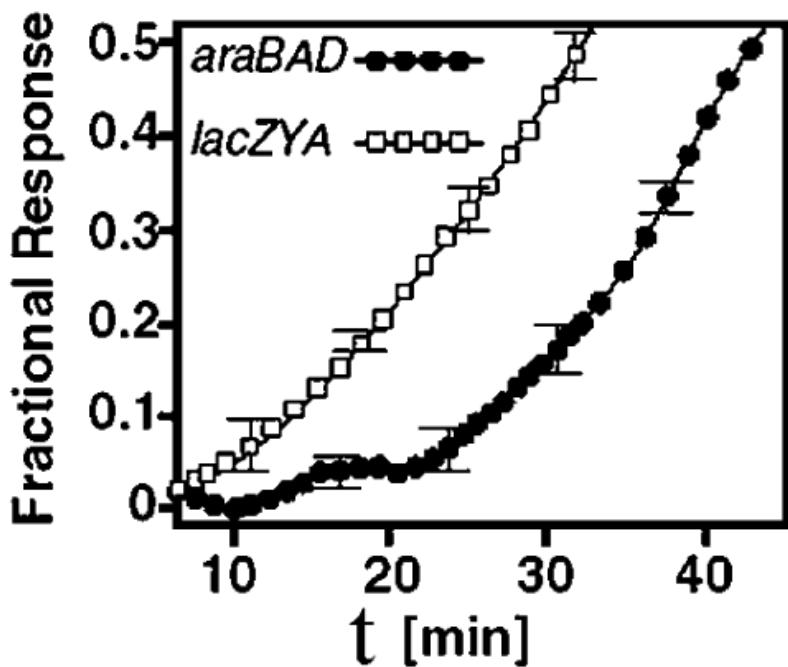


(a) FFL (Ara operon); (b) Simple regulation (Lac operon)

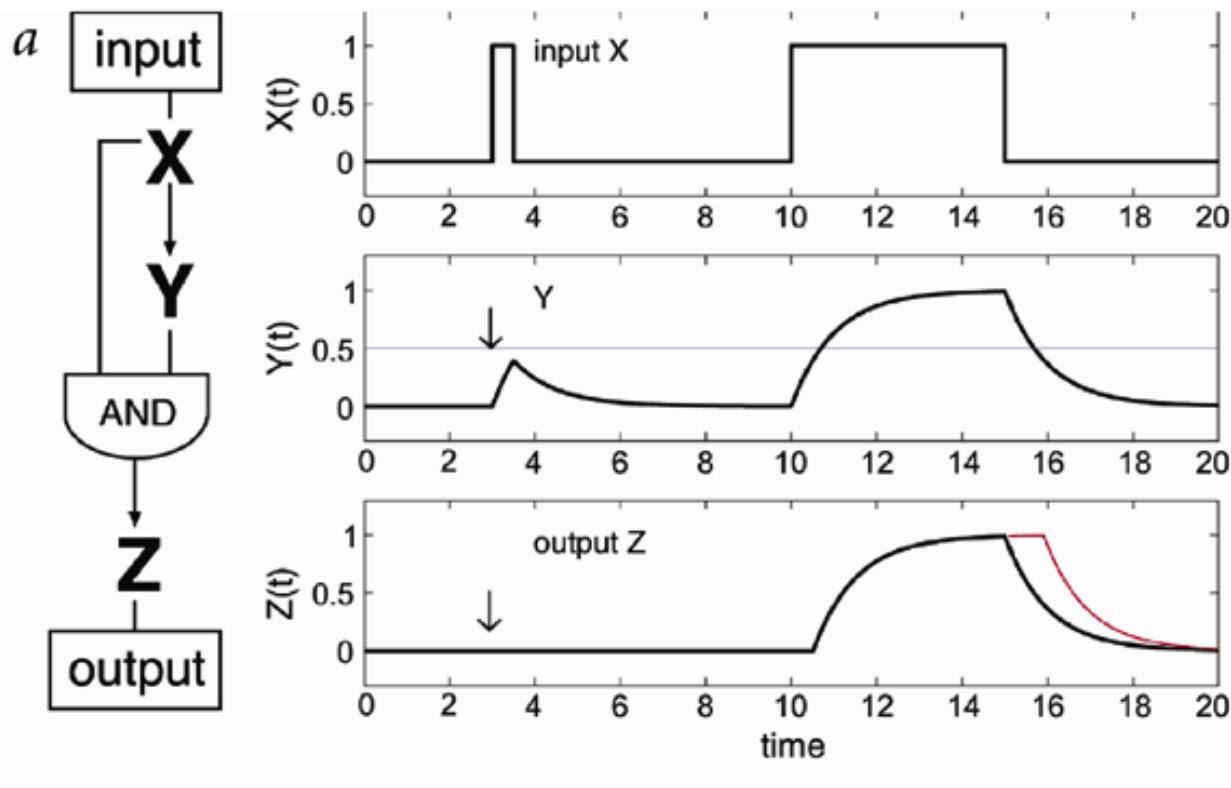
# C1 Feed-forward loop (FFL) vs. simple regulation



# Sign-sensitive delay in FFL

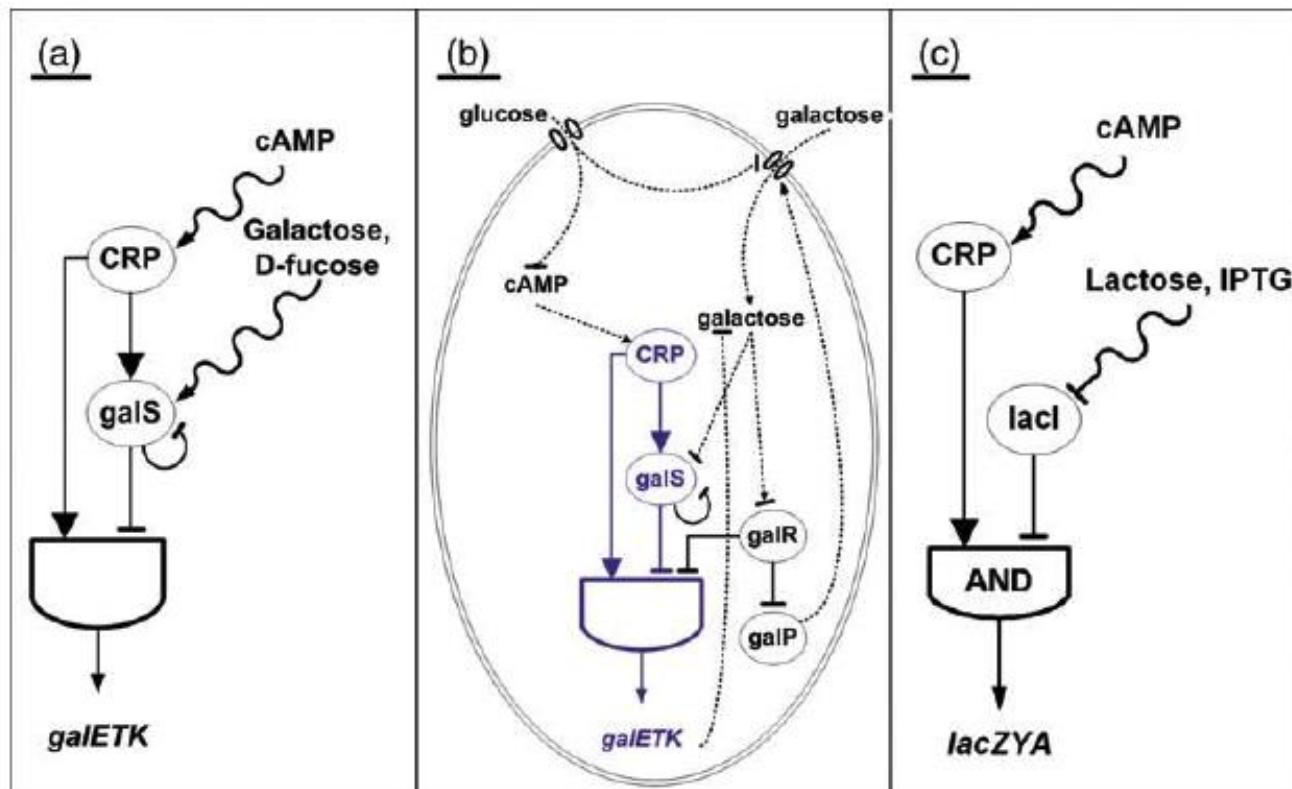


# C1-FFL acts as a Persistent detector



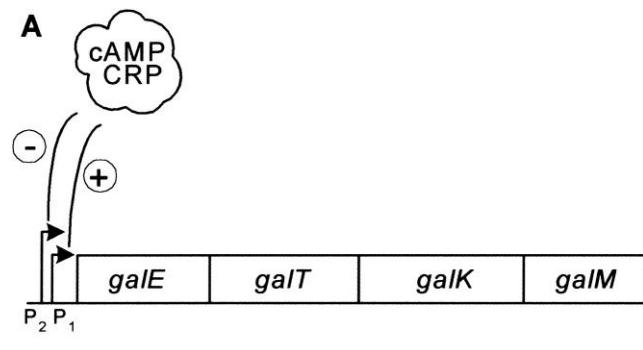
# I1 Feed Forward Loop (FFL)

# Gal operon

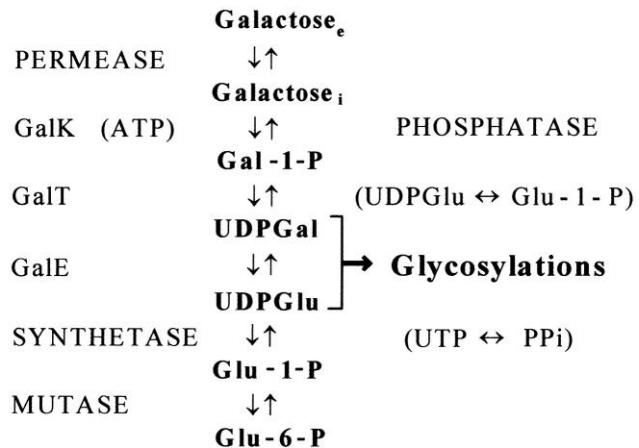


Incoherent FFL (type I)

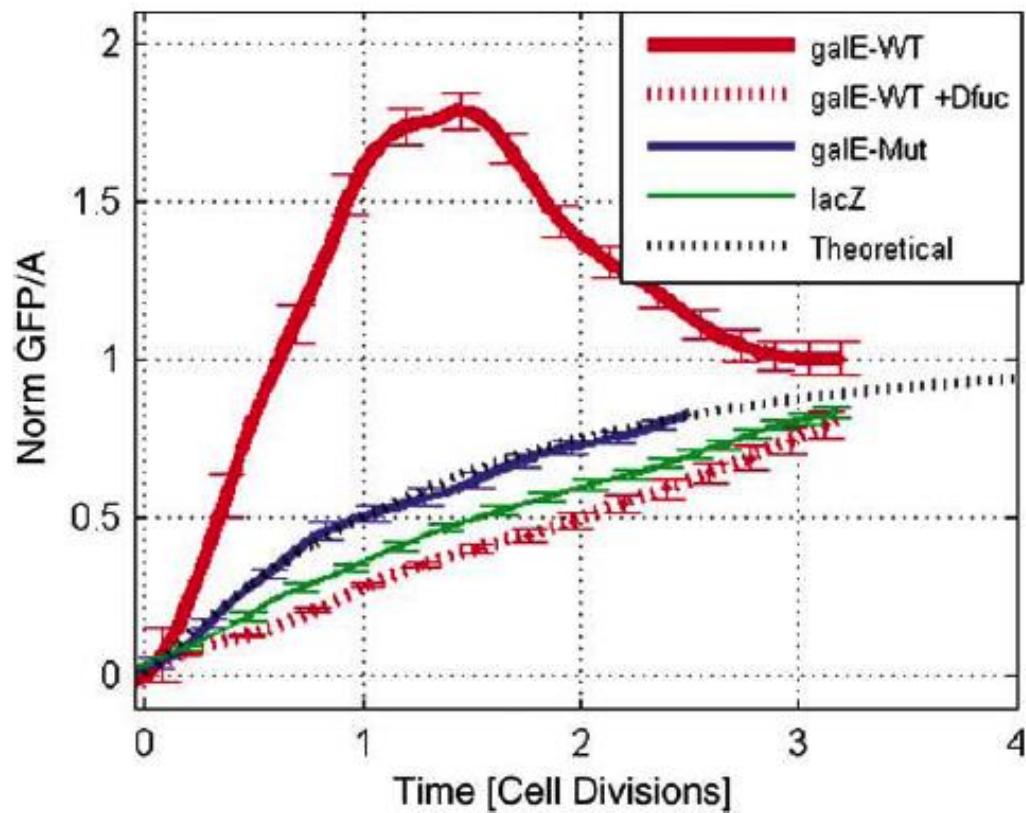
# Gal operon



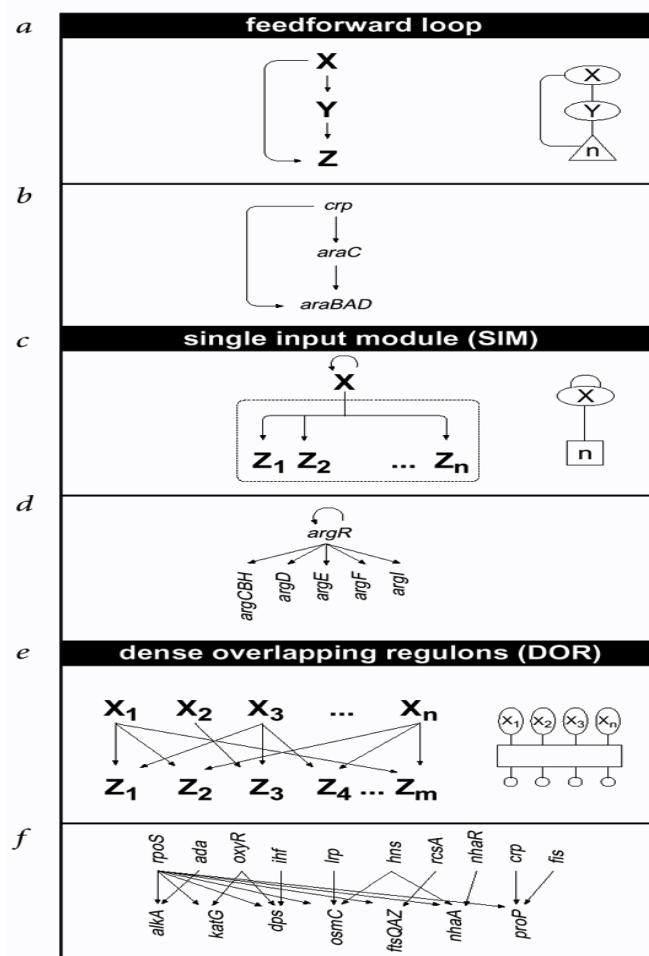
**B**



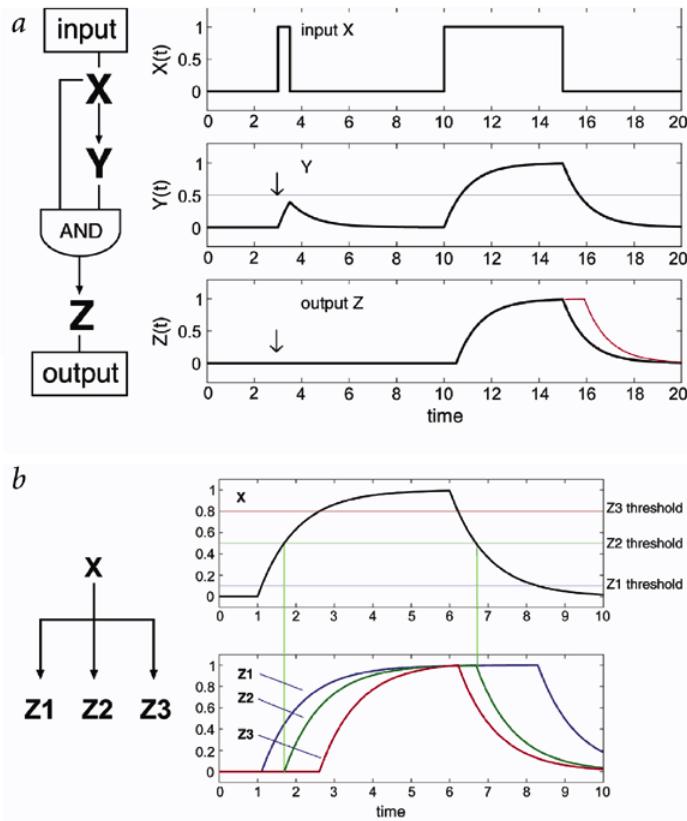
# I1-FFL generates pulse



# Network motifs in the transcriptional regulation network of E. coli



# Different motifs have different dynamical behaviors



# These motifs are enriched in biological network

**Table 1 • Statistics of occurrence of various structures in the real and randomized networks**

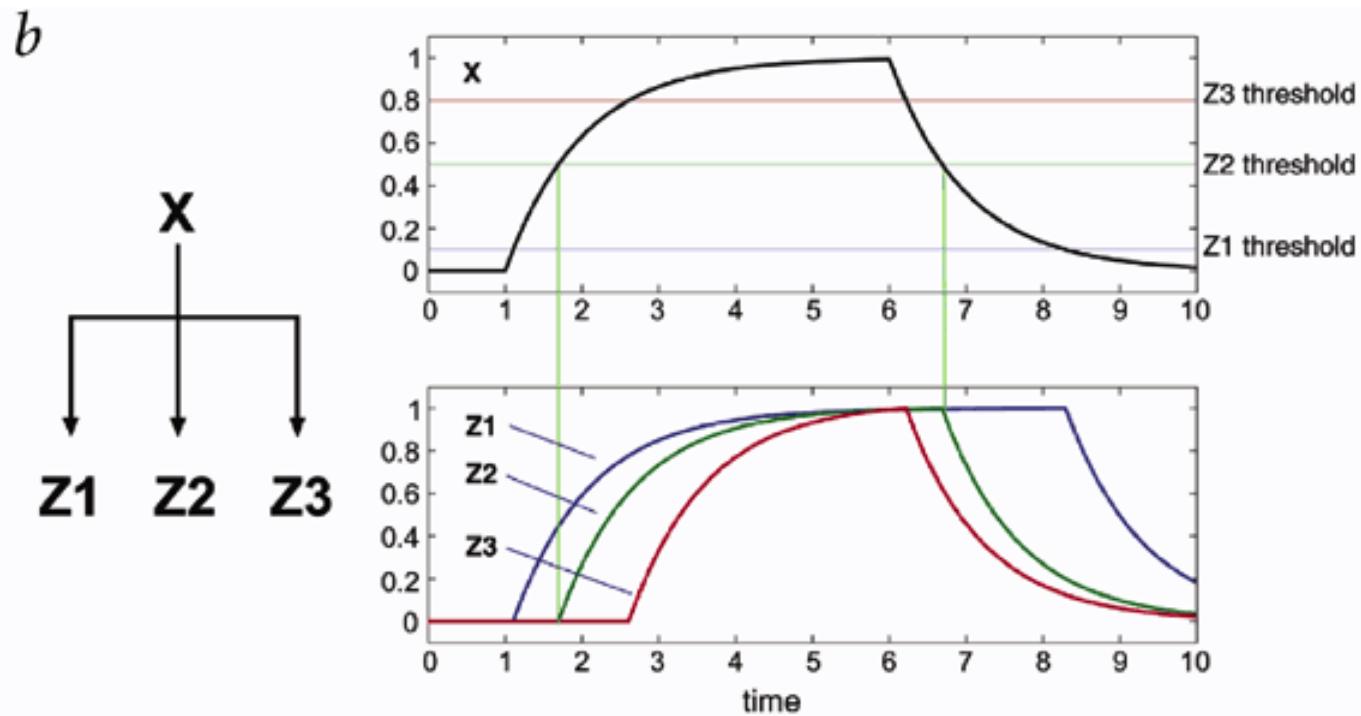
Structure	Appearances in real network	Appearances in randomized network (mean $\pm$ s.d.)	P value
Coherent feedforward loop	34	$4.4 \pm 3$	$P < 0.001$
Incoherent feedforward loop	6	$2.5 \pm 2$	$P \sim 0.03$
Operons controlled by SIM (>13 operons)	68	$28 \pm 7$	$P < 0.01$
Pairs of operons regulated by same two transcription factors	203	$57 \pm 14$	$P < 0.001$
Nodes that participate in cycles*	0	$0.18 \pm 0.6$	$P \sim 0.8$

\*Cycles include all loops greater than size 1 (autoregulation). P value for cycles is the probability of networks with no loops.

# Single-Input Module (SIM)

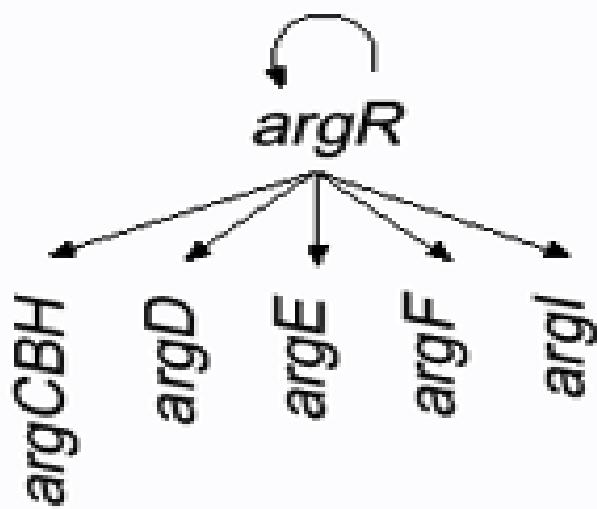
- Single-Input Module (SIM) leads to First In Last Out (FILO).

# Single-Input Module (SIM) motif gives temporal order

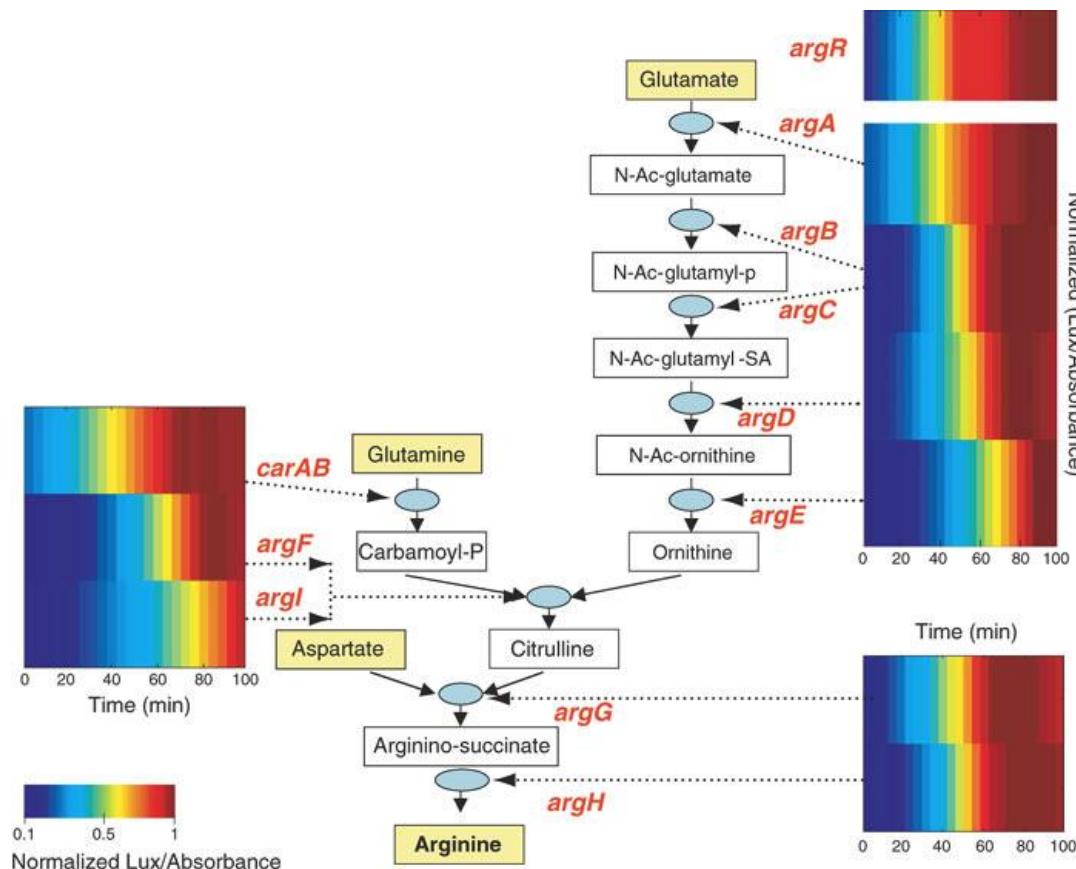


Last In First Out (LIFO)

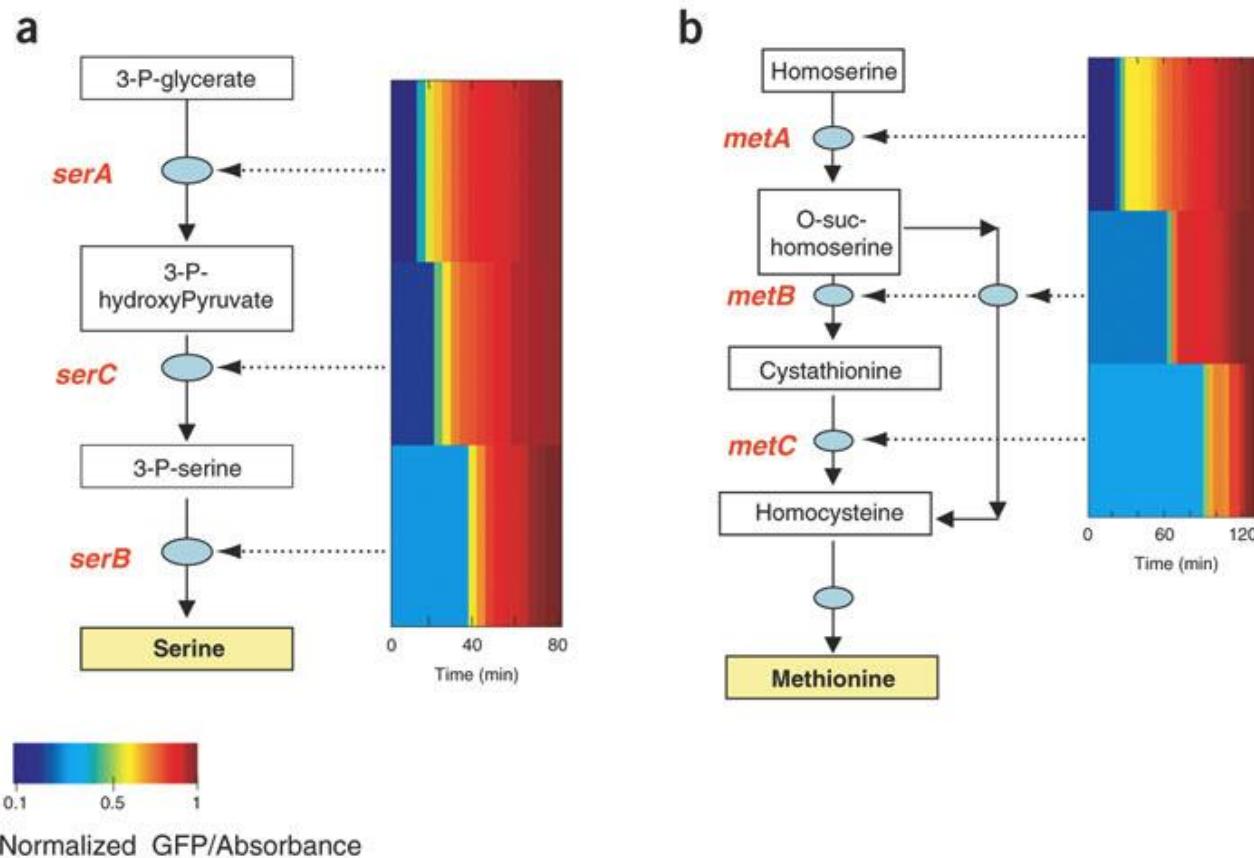
# Arg operon (SIM)



# Single-Input Module (SIM) motif gives temporal order



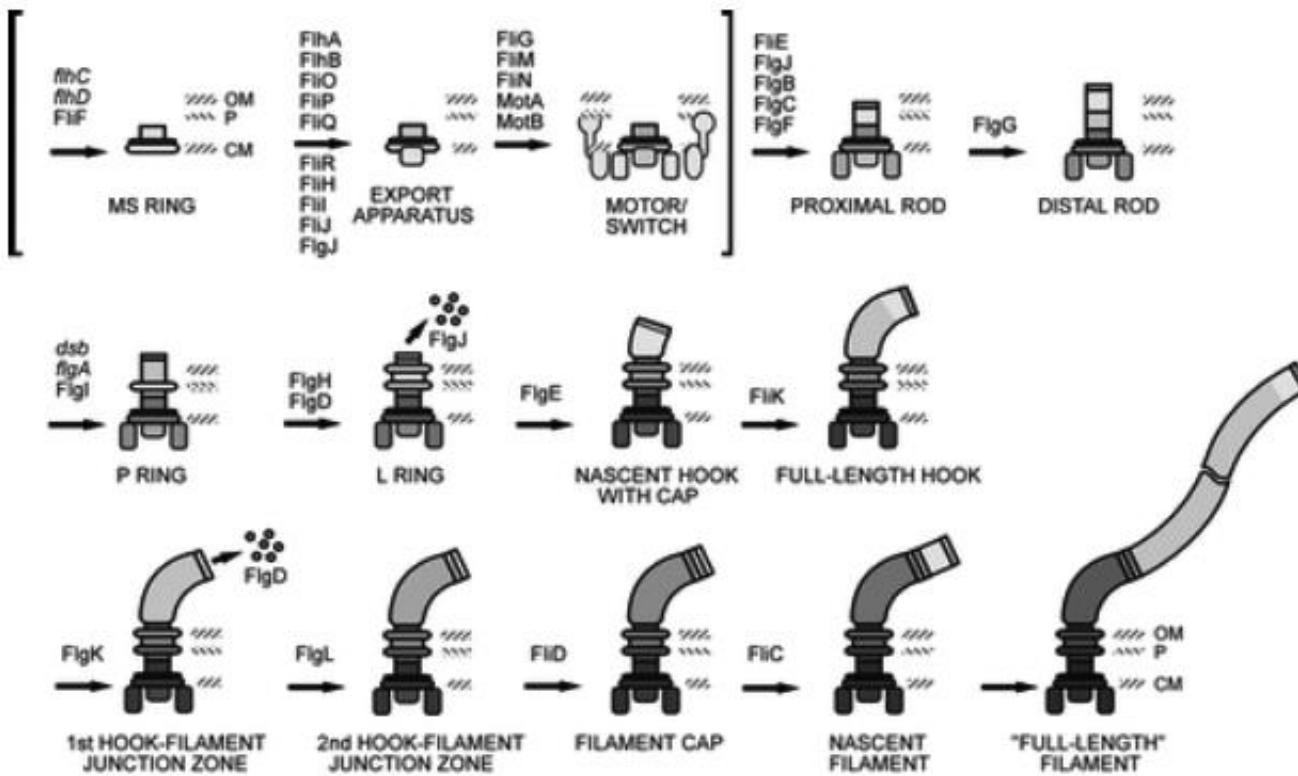
# Single-Input Module (SIM) motif gives temporal order



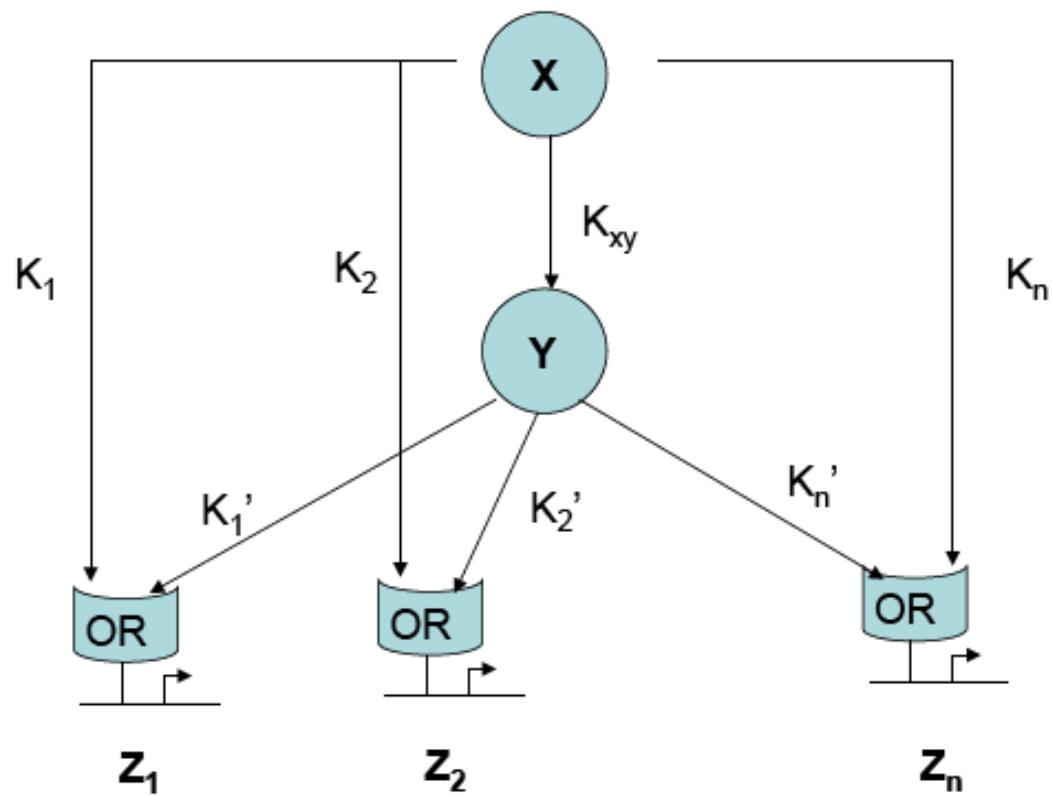
# Multiple output FFL

- Multiple output FFL leads to First In First Out (FIFO).

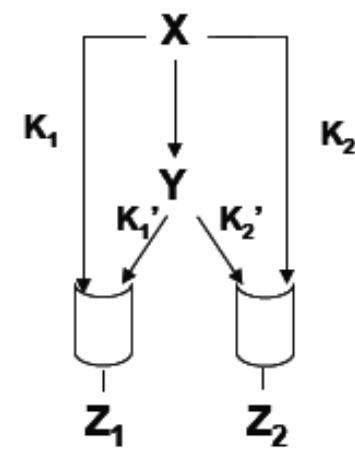
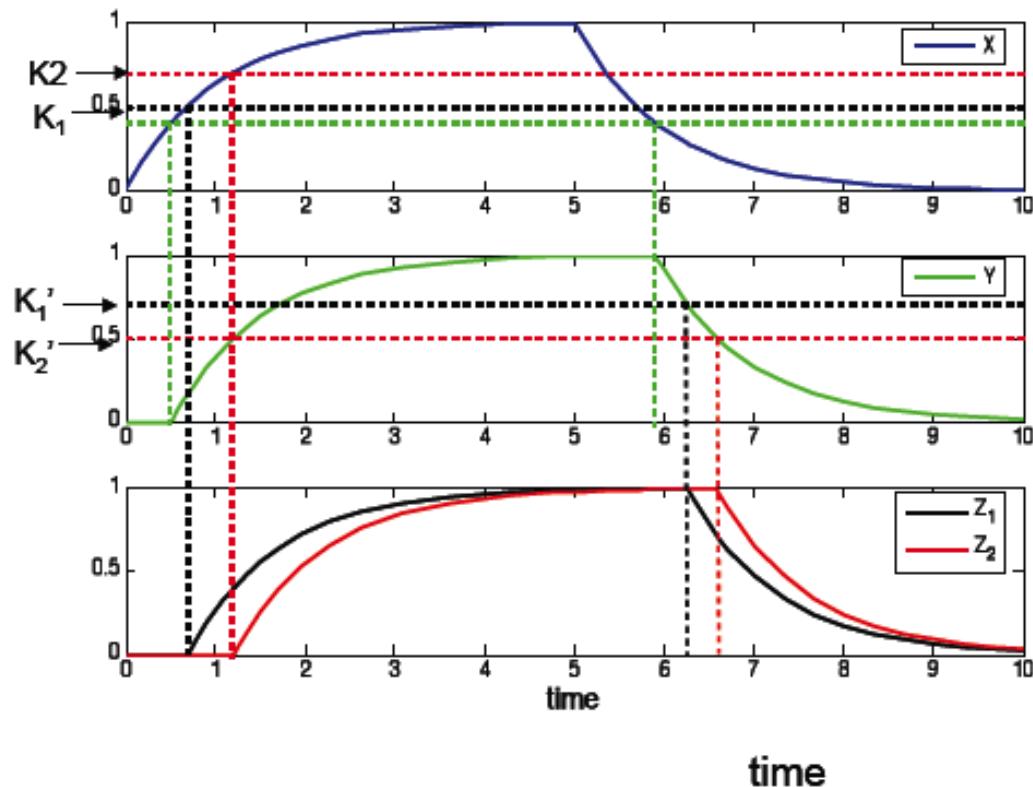
# Flagella assembly



# Multi-output FFL



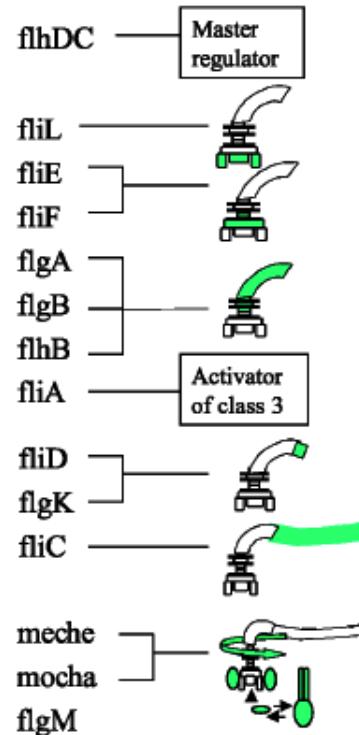
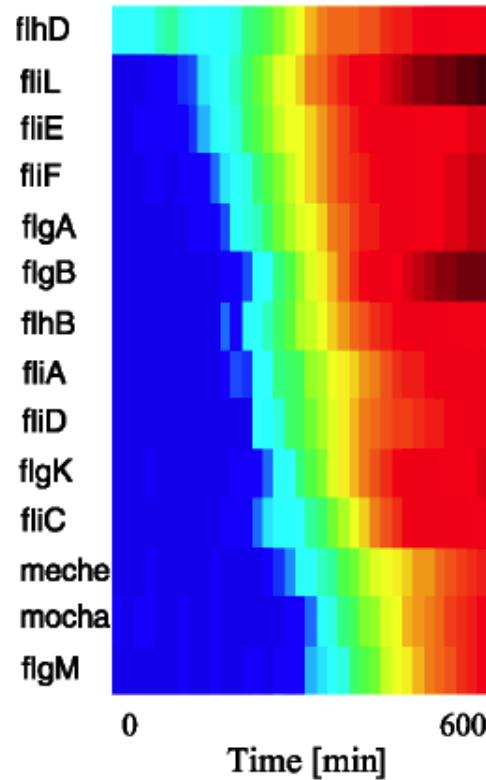
# Multi-output FFL generates First in First Out



$$K_1 < K_2$$

$$K'_1 > K'_2$$

# Multi-output FFL generates First in First Out

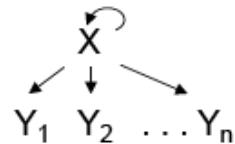


# Summary

Negative Auto-regulation		speeds response time, steady-state robust to fluctuations in production
Positive Auto-regulation		Slows response time Possible bi-stability
Coherent Feed-forward loop		Sign-sensitive delay Filters out brief ON (OFF) input pulses when the Z-input function Is AND (OR) logic.
C1- FFL		Pulse generation Signs-sensitive Response acceleration
Incoherent Feed-forward loop		
I1-FFL		

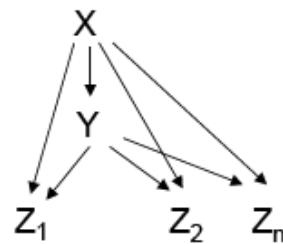
# Summary

Single- Input  
Module (SIM)



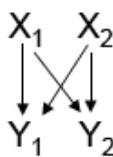
Coordinated control  
Temporal (LIFO) order of  
Promoter activity

Multi-output  
Feed-forward loop  
(multi-output FFL)



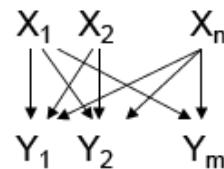
Acts as FFL for each input  
(sign-sensitive delay, etc)  
FIFO temporal order of  
promoter activity

Bifan



Combinatorial logic  
based on multiple inputs,  
depends on  
Input-function of each gene

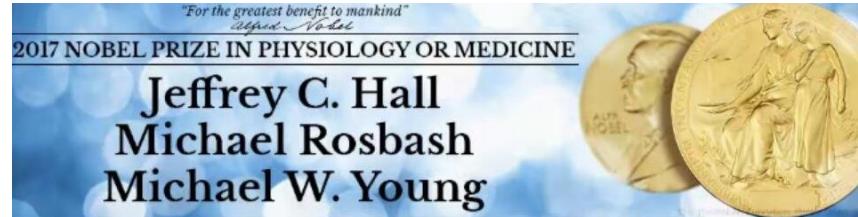
Dense overlapping  
Regulons) DOR(





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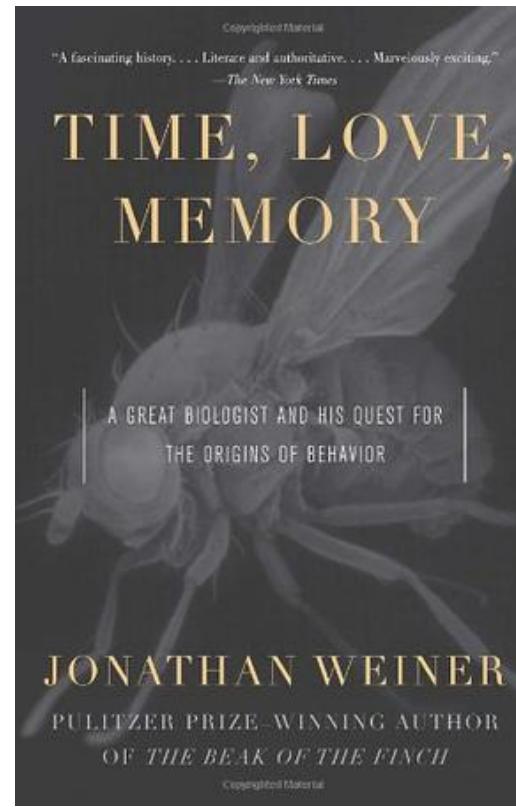
Jeffrey C. Hall,

Michael Rosbash and Michael W. Young. III. Niklas Elmehed.  
© Nobel Media 2017.

## 2017 Nobel Prize in Physiology or Medicine

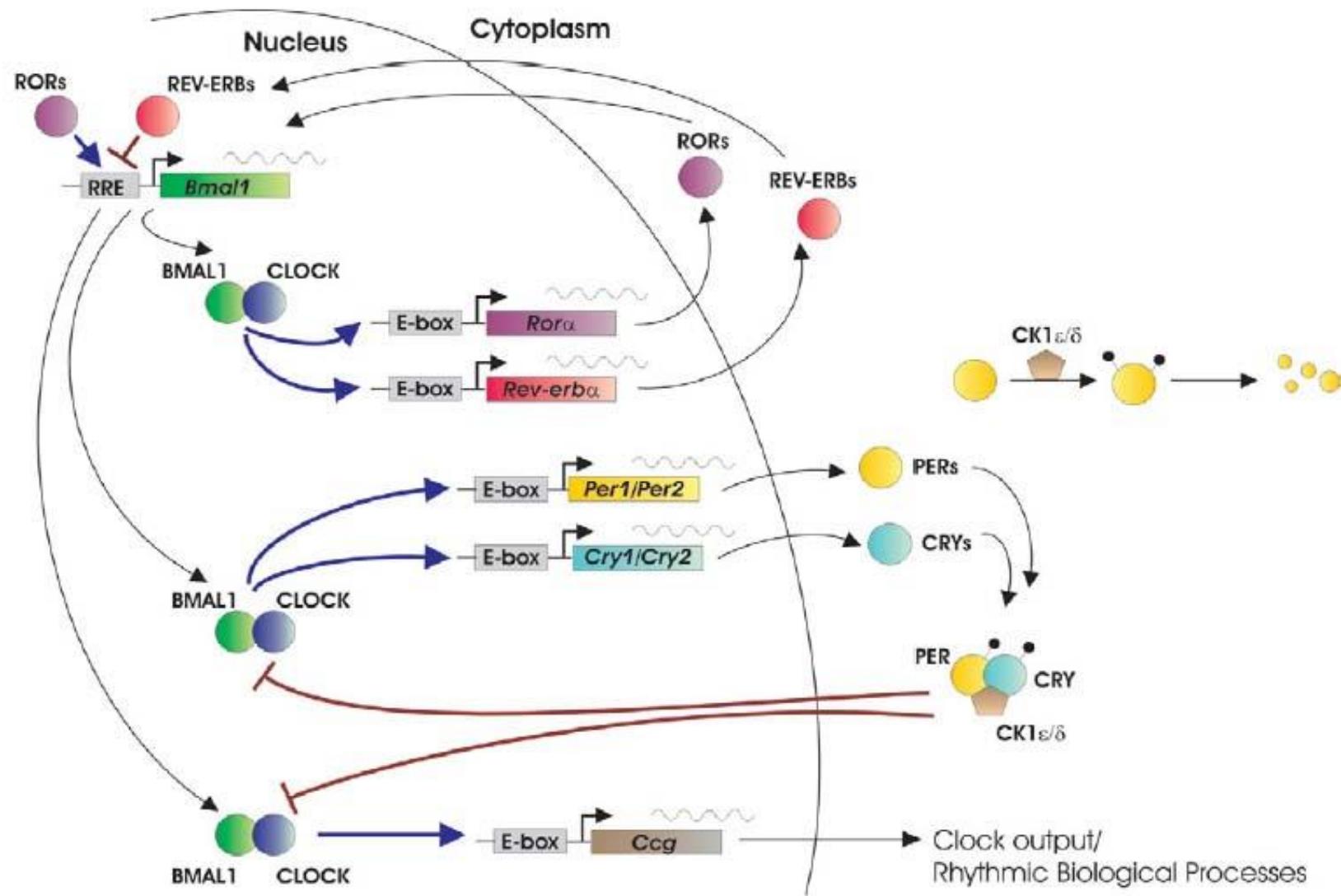
The Nobel Prize in Physiology or [Medicine](#) 2017 was awarded to Jeffrey C. Hall, Michael Rosbash and Michael W. Young "for their discoveries of molecular mechanisms controlling the circadian rhythm".

# 生物钟基因的发现



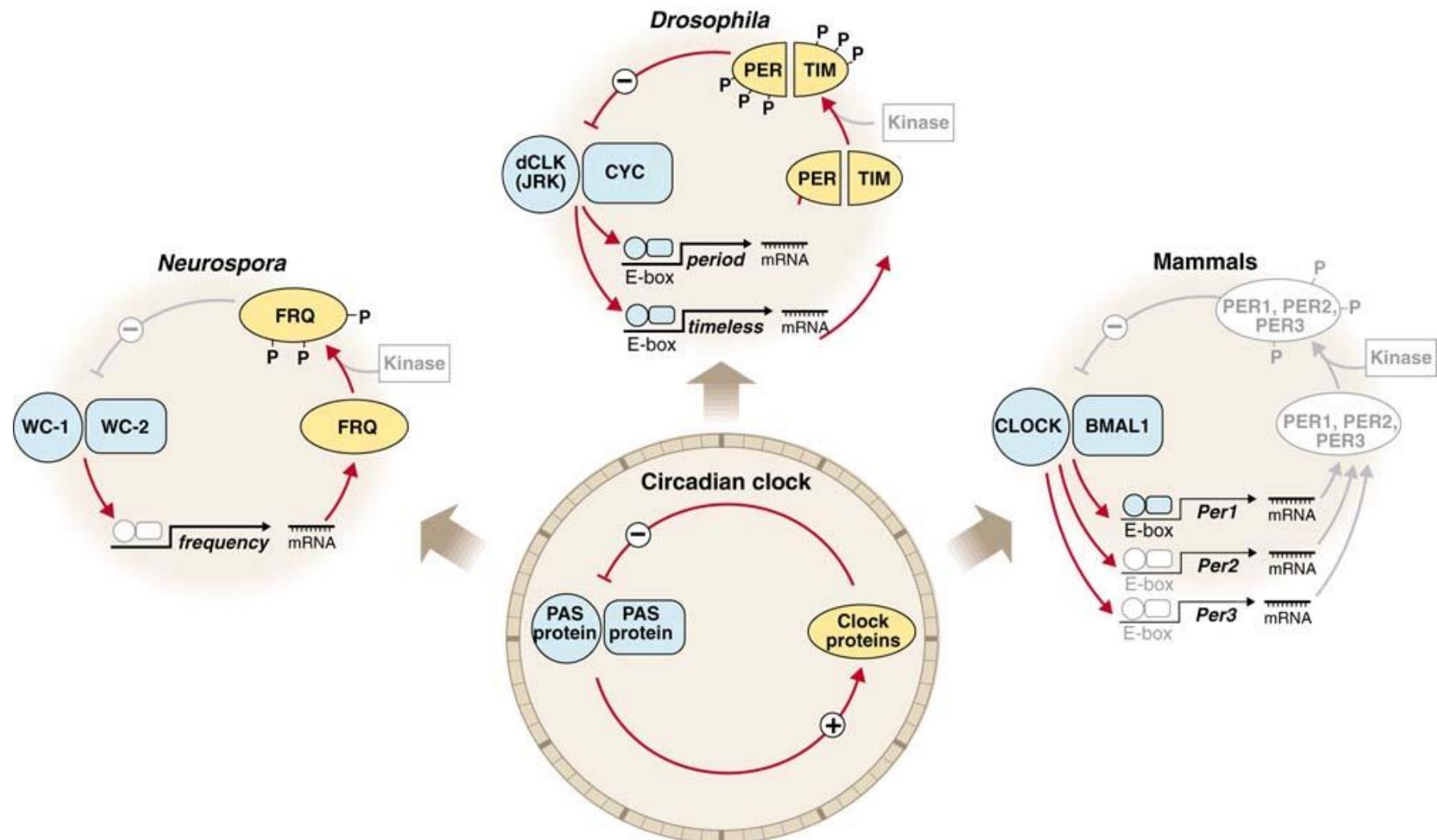
**Seymour Benzer (1921 – 2007)**

# Molecular components of the mammalian circadian clock



Ko CH, Takahashi JS (2006) Hum Mol Genet. 15 Sp

# Conservation of Clock Mechanism



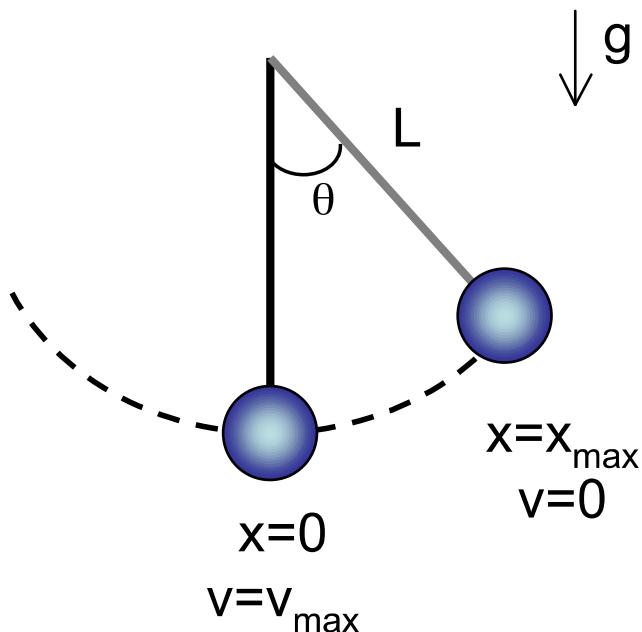
Dunlap J Science 280(5369):1548-9 (1998).



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## 钟摆模型：谐振子



$$\frac{d^2\theta}{dt^2} + \frac{g}{L} \theta = 0$$

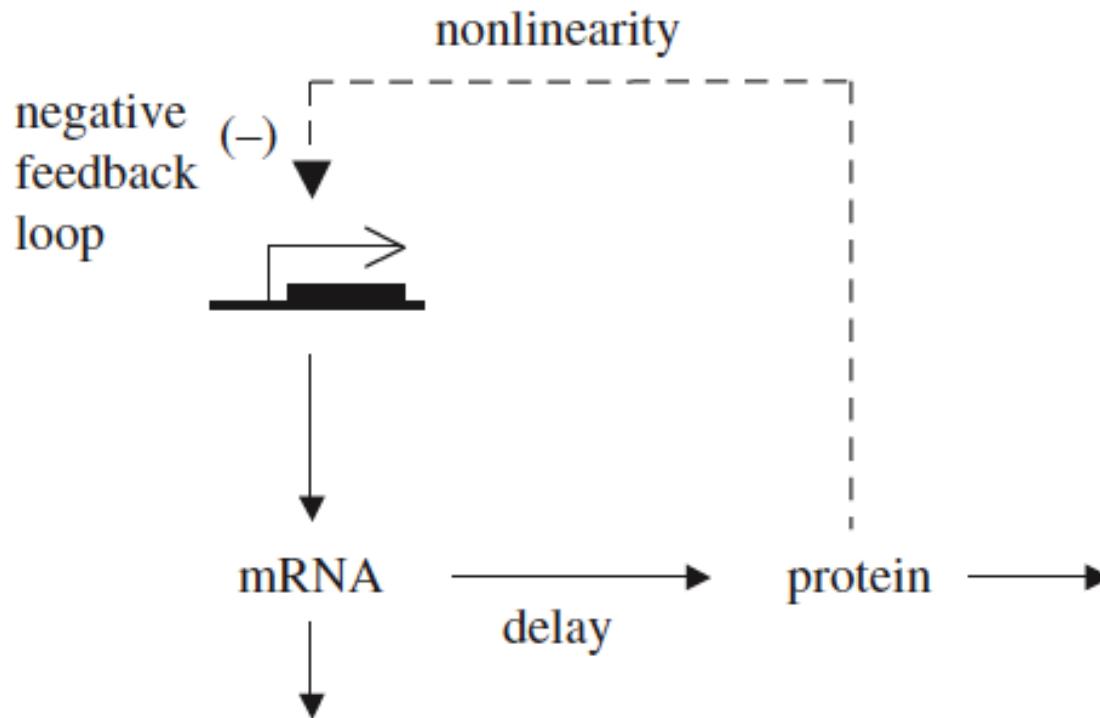
$$\theta(t) = \theta_0 \cos\left(\sqrt{\frac{g}{L}} t\right)$$



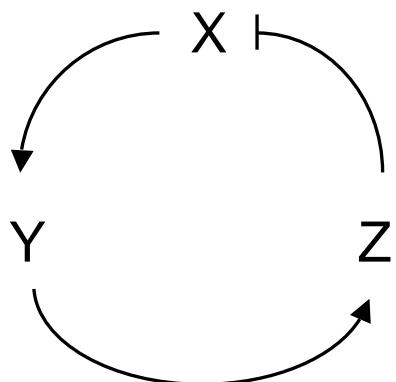
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## 基因调控网络

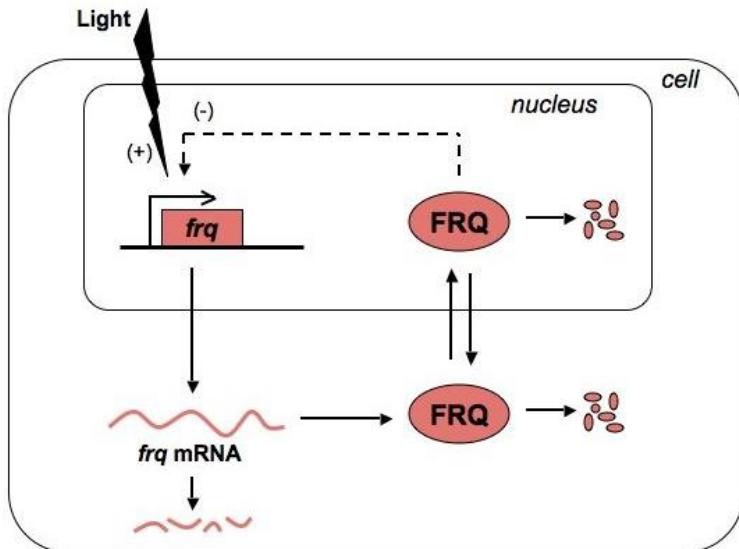


# Goodwin model



$$\begin{aligned}\frac{dX}{dt} &= k_1 \frac{1}{K_I^n + Z^n} - k_2 X \\ \frac{dY}{dt} &= k_3 X - k_4 Y \\ \frac{dZ}{dt} &= k_5 Y - k_6 Z\end{aligned}$$

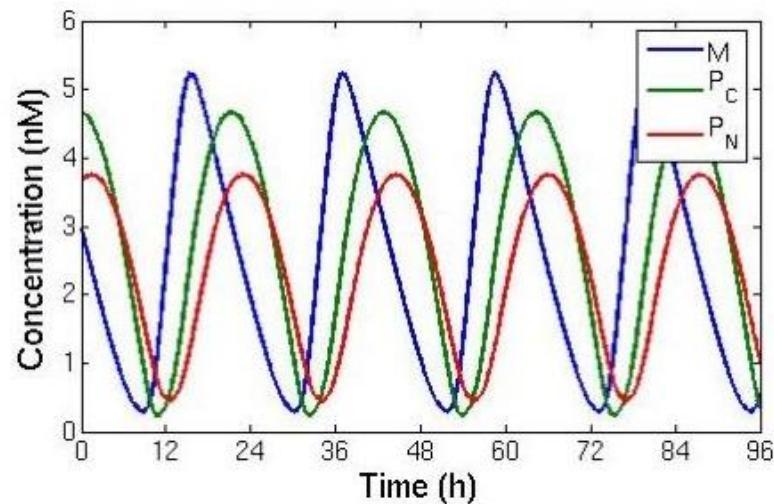
# 昼夜节律模型



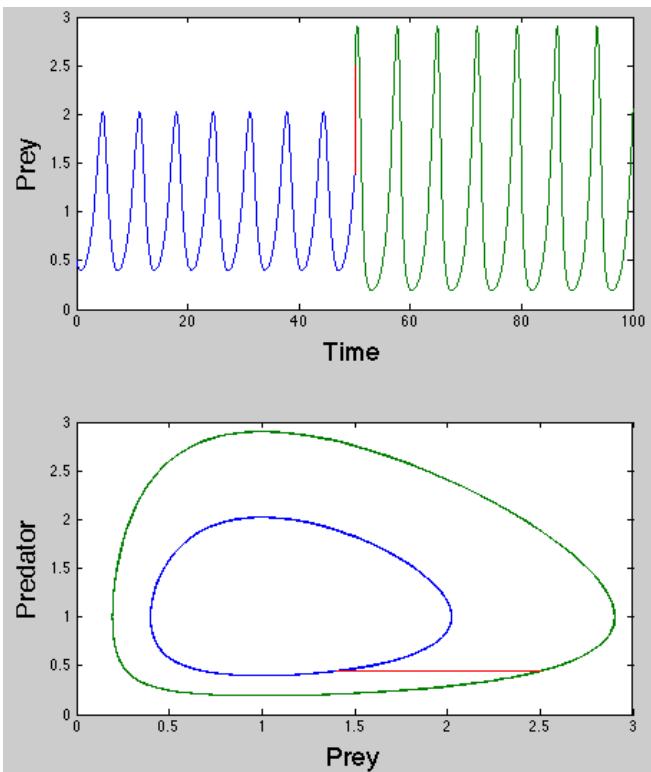
$$\frac{dM}{dt} = v_s \frac{K_I^n}{K_I^n + F_N^n} - v_m \frac{M}{K_m + M}$$

$$\frac{dF_C}{dt} = k_s M - k_1 F_C + k_2 F_N - v_d \frac{F_C}{K_d + F_C}$$

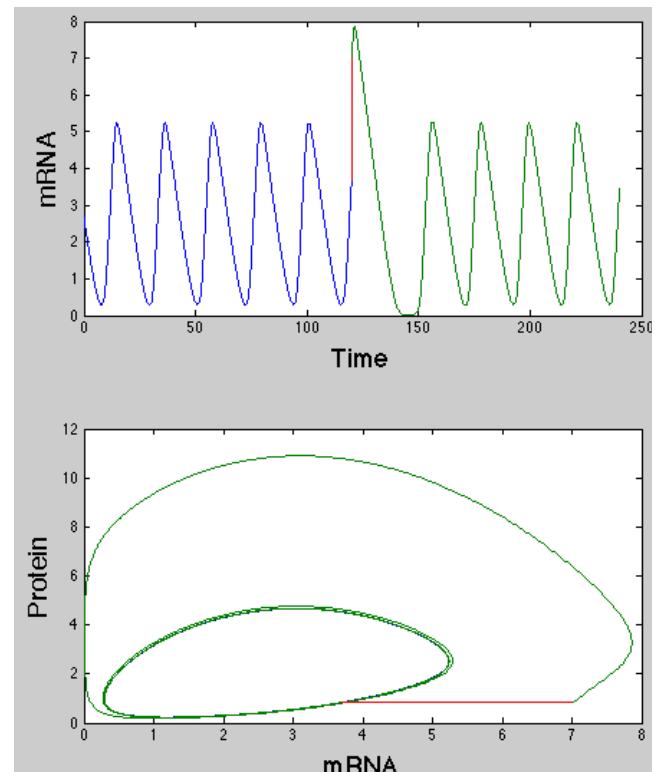
$$\frac{dF_N}{dt} = k_1 F_C - k_2 F_N - v_n \frac{F_N}{K_n + F_N}$$



# 昼夜节律模型与钟摆模型的差别

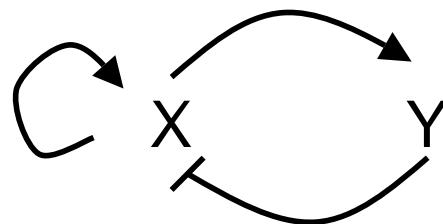
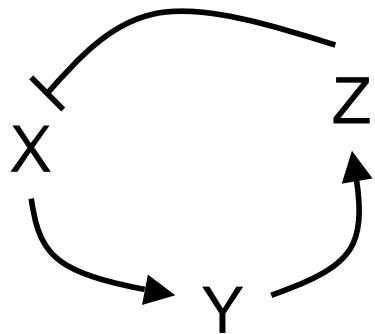


钟摆模型



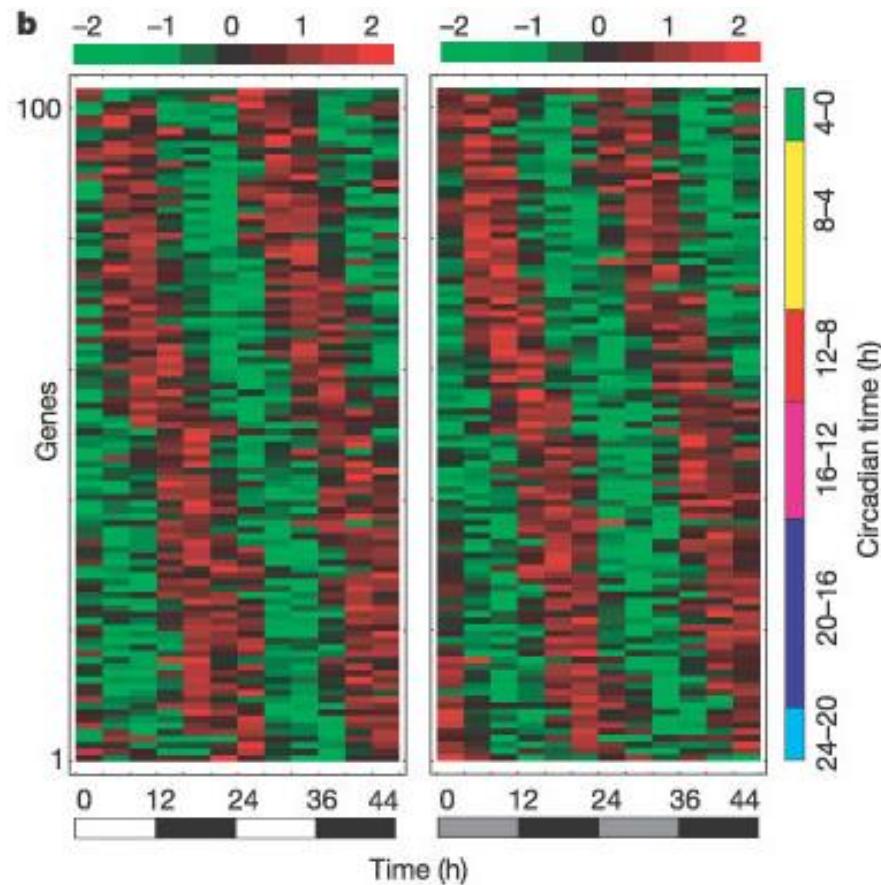
节律模型

# 怎样造一个生物钟？



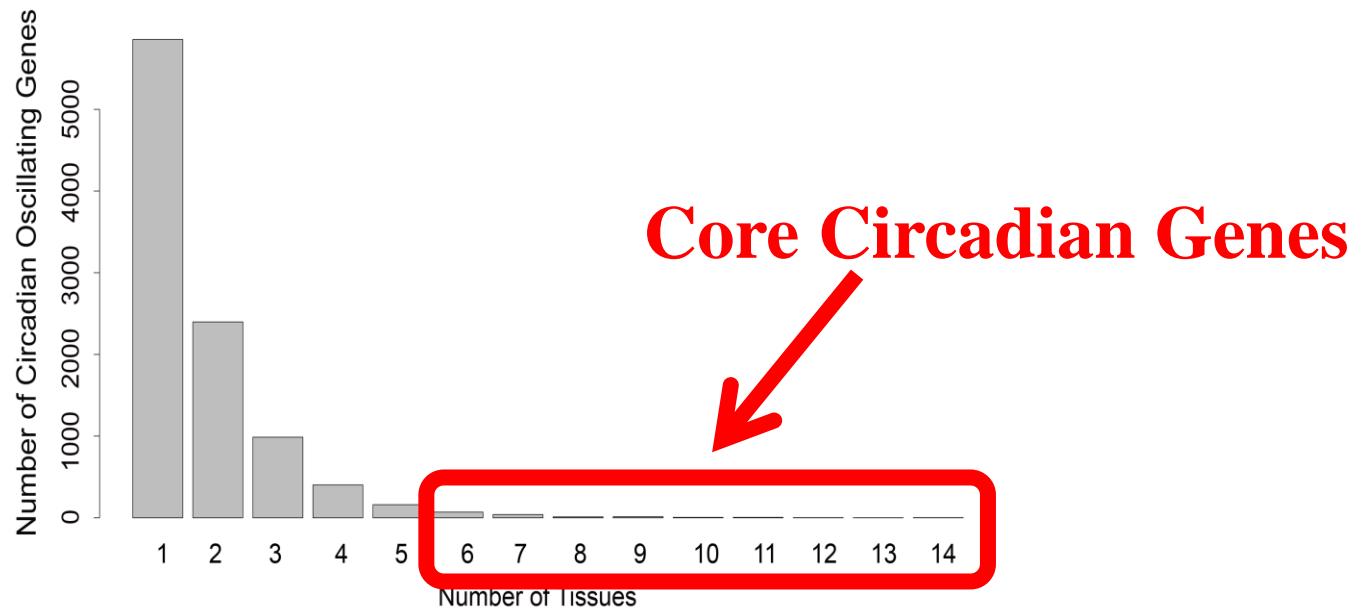
1. 负反馈
2. 时间延迟（或正自反馈）
3. 非线性

# Circadian Gene Expression



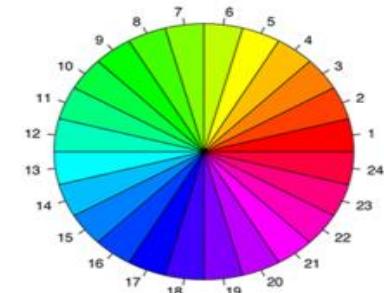
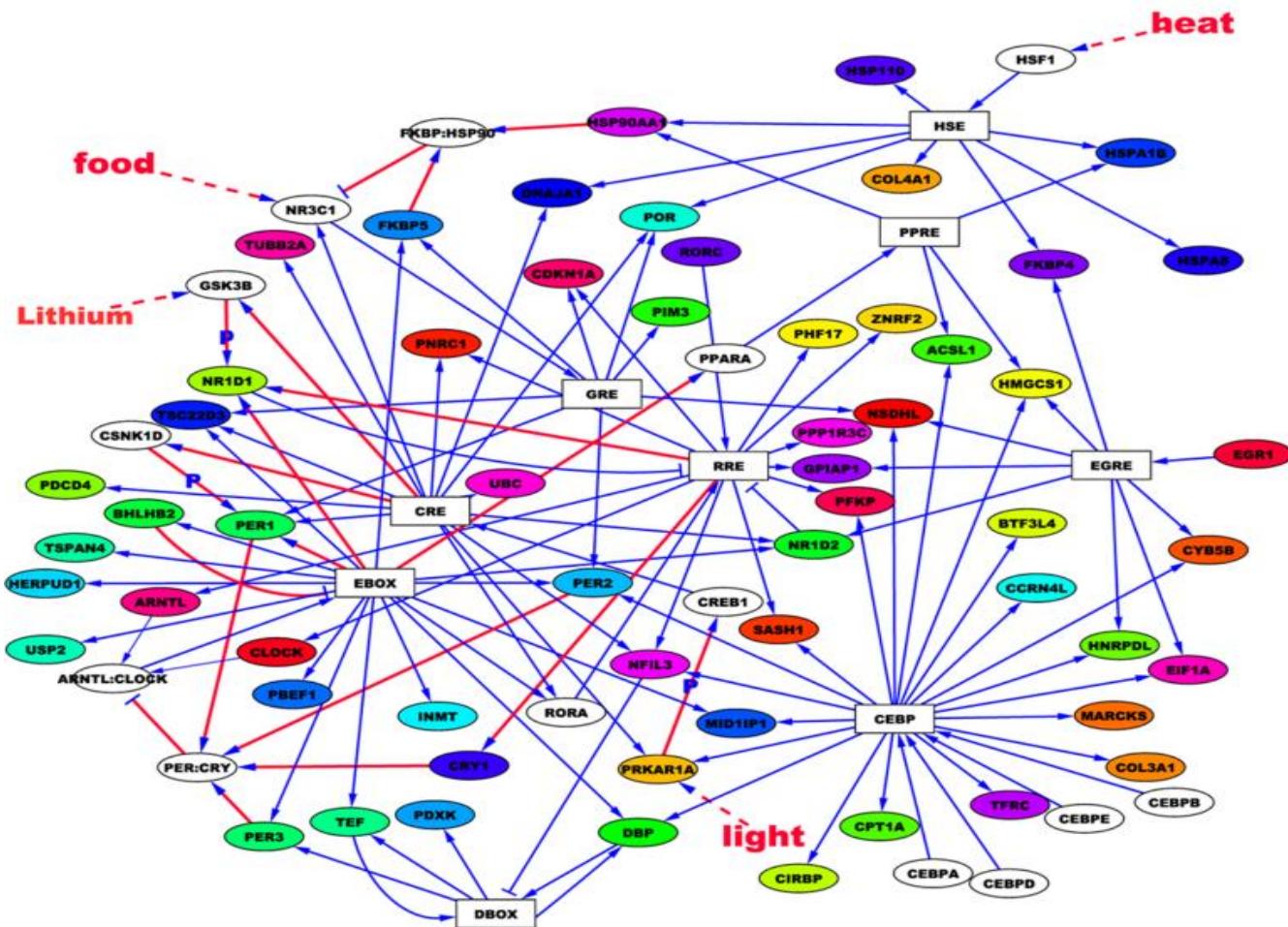
Ueda et al. *Nature* **418**, 534-539, 2002

## Diverse tissue-specific circadian gene expression

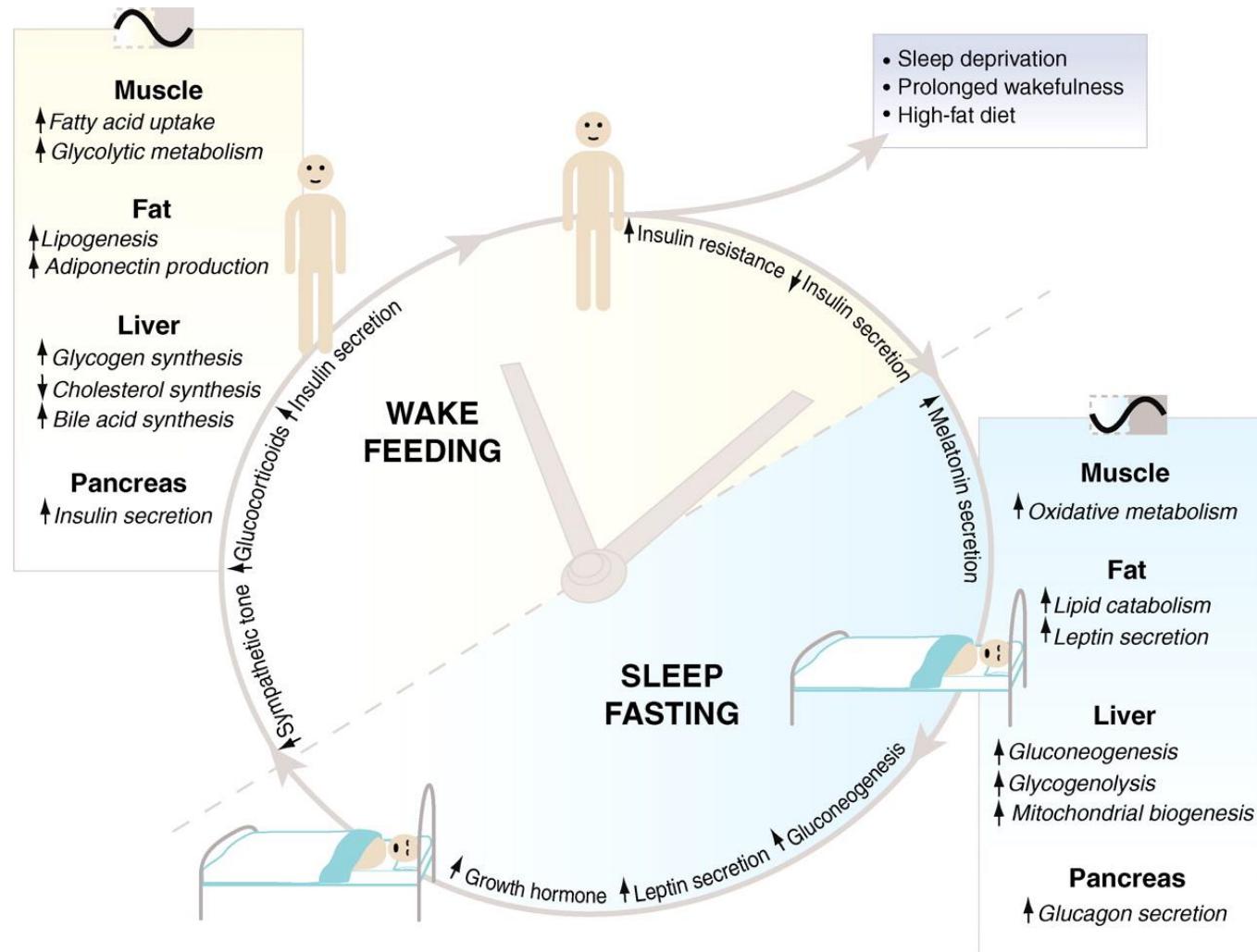


Yan et al., *PLoS Comp Biol*, 4: e1000193, 2008.

# Circadian transcriptional regulatory network in mouse



# The clock partitions behavioral and metabolic processes according to time of day.



J Bass, and J S Takahashi Science 2010;330:1349-1354