Chapter 6: Regulatory Networks

6.1 Introduction To Regulatory Networks

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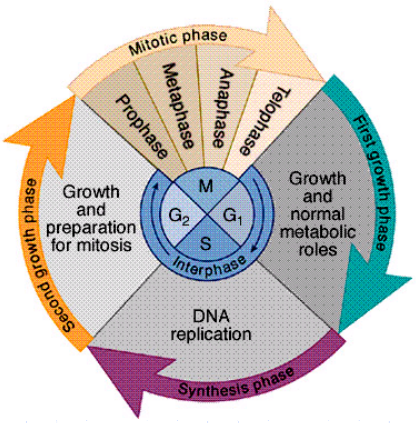
Overview

- Transcription & regulation mechanisms
- Regulatory network structures (gene circuits)

Regulatory Mechanisms

Cells Must Regulate Internal Processes

- Metabolic processing
- Cell cycle functions
  - Growth
  - DNA replication/repair
  - Mitosis
  - Preparation phases
- These require careful control of gene expression
  - Expression level
  - Timing
  - Coordination



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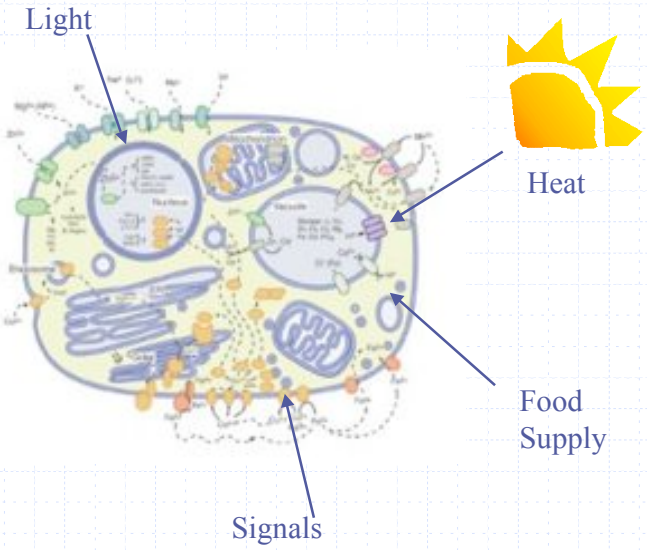
Cells Must Adapt To Their Environment



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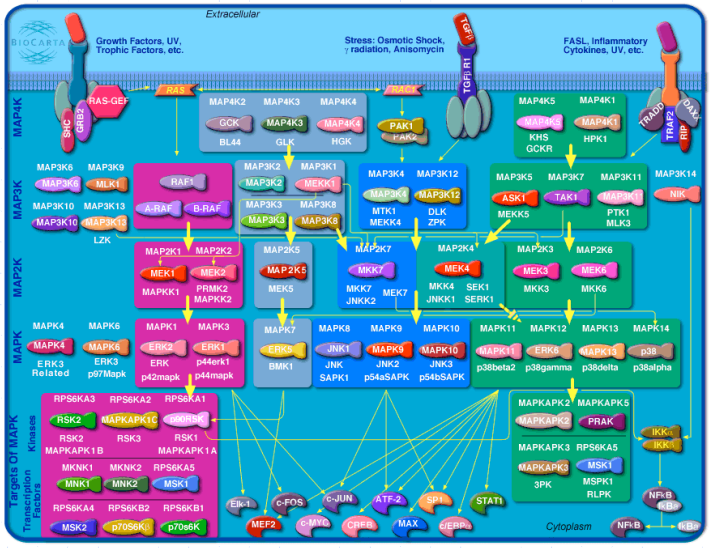
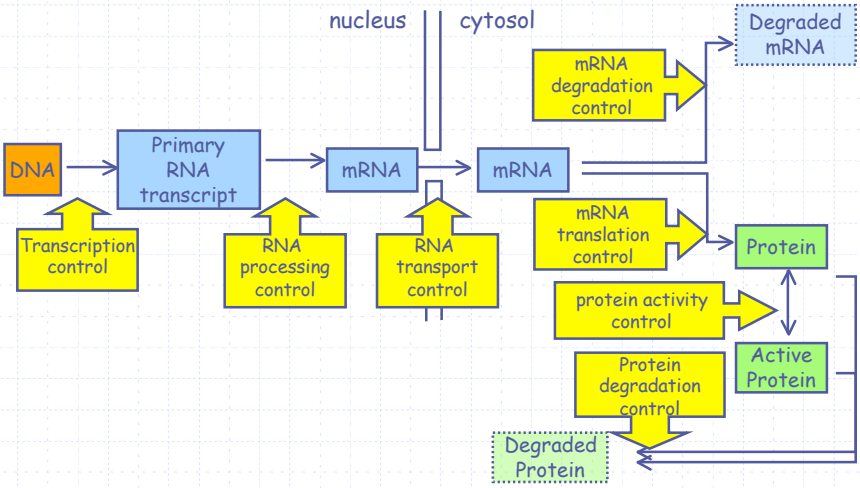
Cell Activities Are Organized Into Pathways



http://www.biocarta.com/genes/PathwayGeneSearch.asp?geneValue=g

6

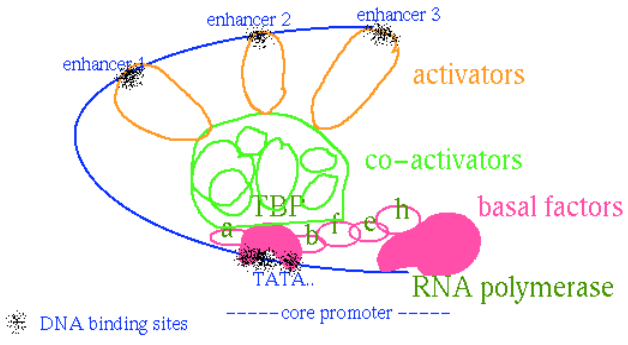
Regulation



7

Regulating Transcription Is A Key Construct

- Transcription factors (TF) regulate transcription
  - Promoters control transcription initiation (cis-regulation)
  - Enhancers control transcription from afar (trans-regulation)
- Most genes are involved in regulation



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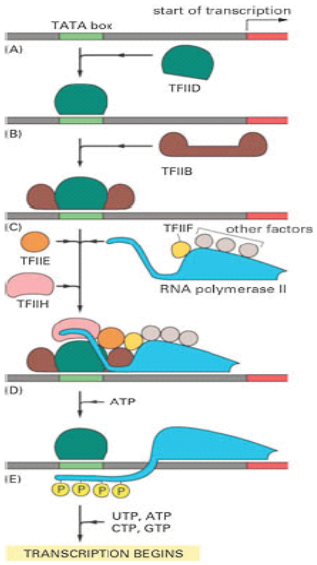
Regulation Mechanics

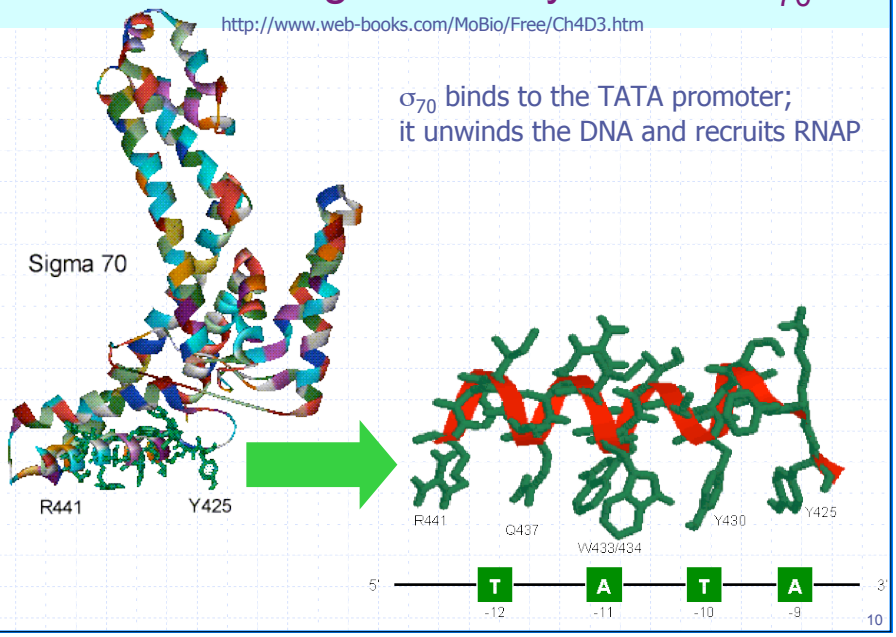
- TFs bind to promoters/silencer regions and to RNAP polymerases
- TFs regulate transcription rate



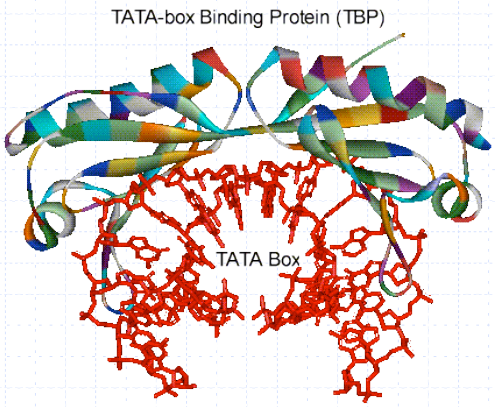
TATA Binding in Prokaryotes: TF σ_{70}

http://www.web-books.com/MoBio/Free/Ch4D3.htm

σ_{70} binds to the TATA promoter;
it unwinds the DNA and recruits RNAP

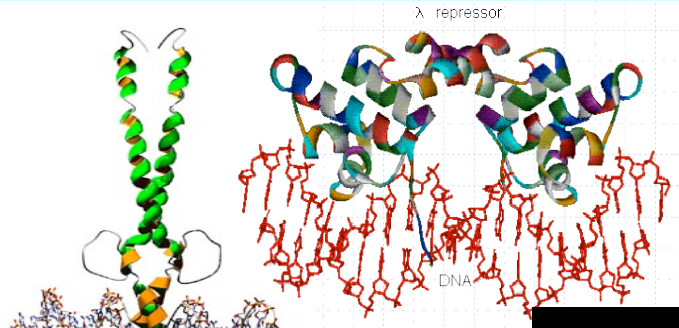


TATA Binding in Eukaryotes



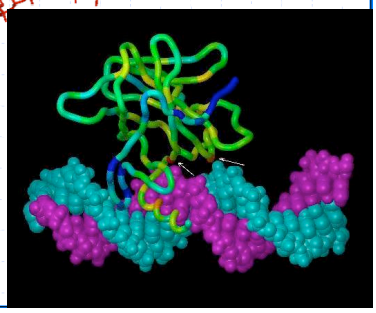
11

Examples of TF Structures



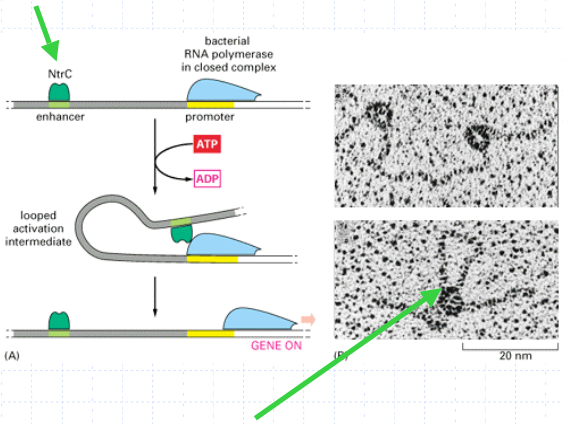
bHLH-Zip domain

P53



Distant Regulation By Enhancers

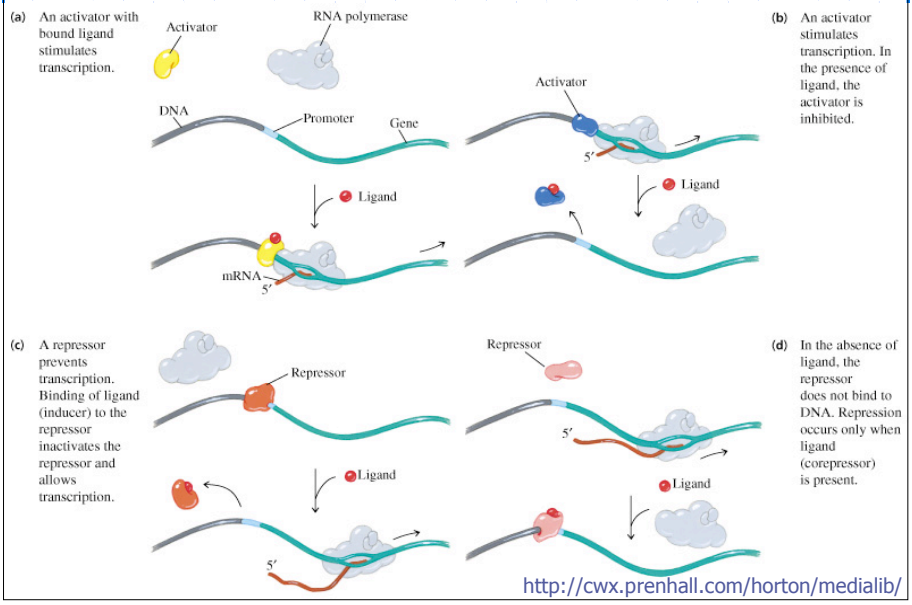
Nitrogen Regulatory protein C



DNA loops to facilitate NTRC-RNAP interactions

13

Activators & Repressors

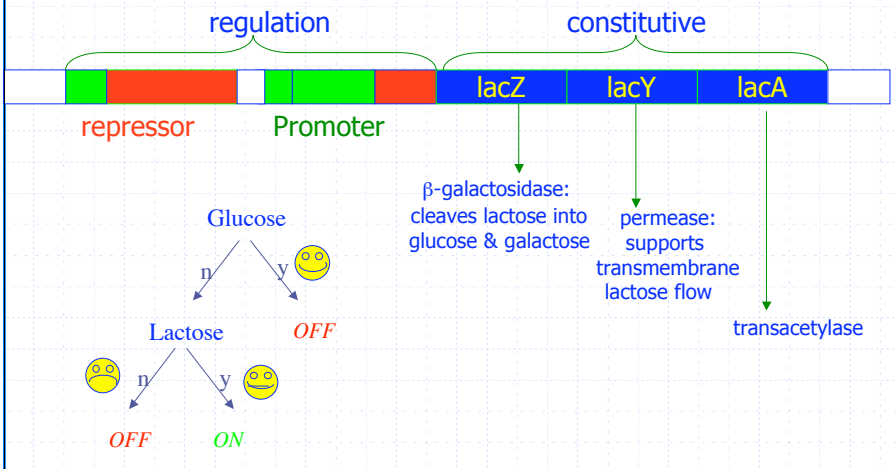


http://cwx.prenhall.com/horton/medialib/

The LAC Operon

J. Monod & F. Jacob 1960's

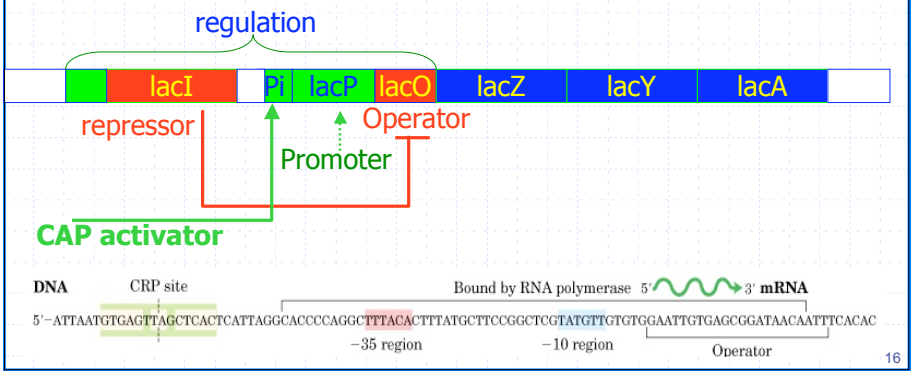
- LacZ and LacY play key role in lactose catabolism
- Regulation: activate/repress Lac to regulate sugar availability



15

The LAC Operon

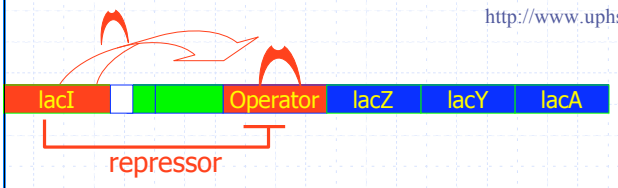
- Operon: a functional genome segment (regulation+functions)
- Monod & Jacob: discovered the regulatory mechanisms
  - Used mutations to investigate regulation
  - Identified promoter/repressor regulation
- Animation site: http://www.youtube.com/watch?v=EsWhrJ51Y6U



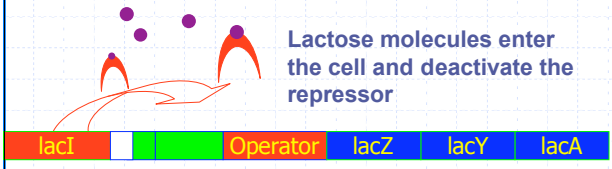
16

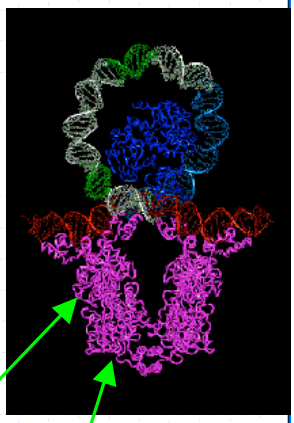
Lac Repression

http://www.uphs.upenn.edu/biocbiop/images.html



Lactose molecules enter the cell and deactivate the repressor





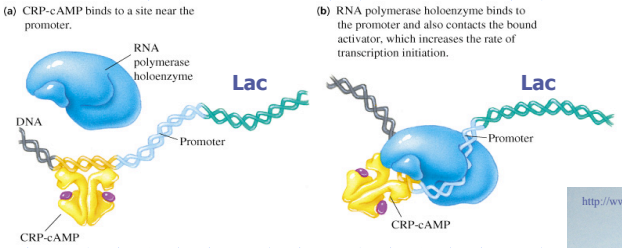
Lactose inducer releases the repressor

The repressor twists the DNA into a loop

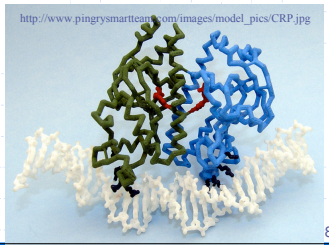
17

Lac Activation

- Low glucose ➔ activates generation of cAMP
- cAMP ➔ binds with CRP; adjusts helix to fit DNA grooves
- CAP=CRP+cAMP ➔ accelerates RNAP binding to promoter



http://cwx.prenhall.com/horton/medialib/



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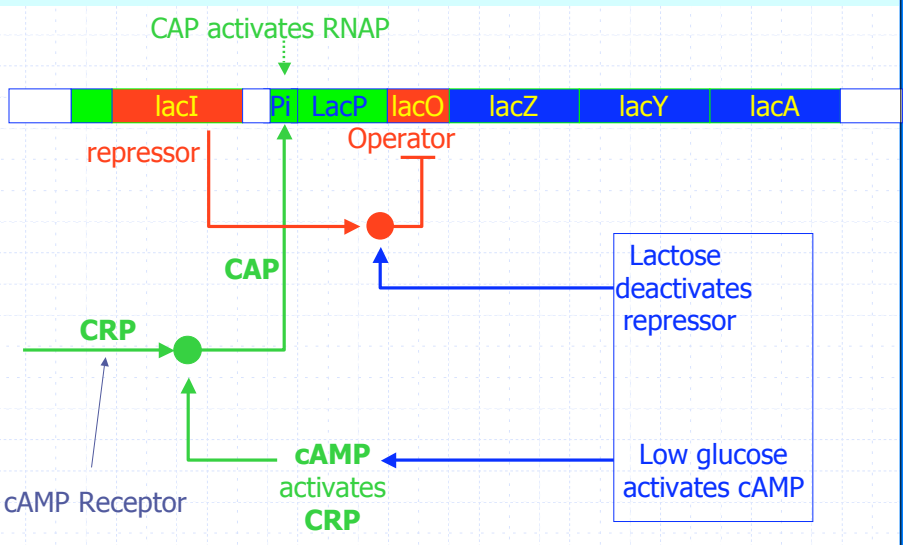
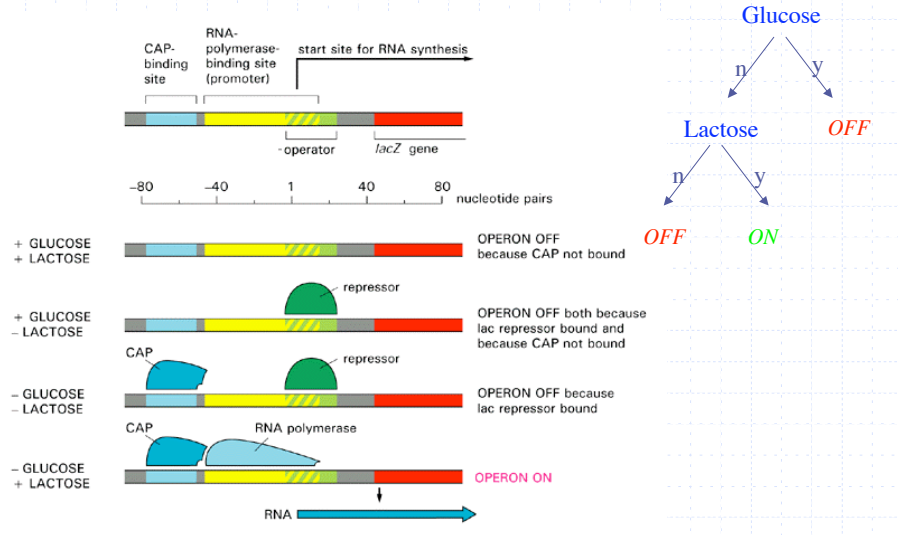
Control Paradigm



Feed forward activation + feedback repression

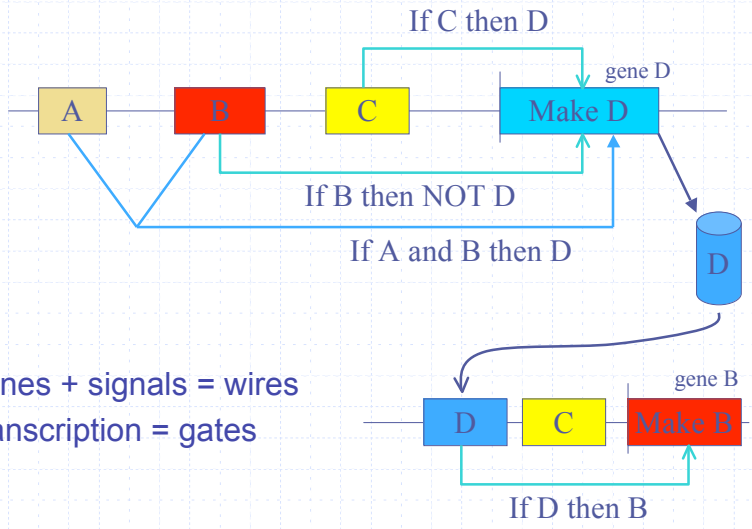
19

The Logic of Lac Operon



20

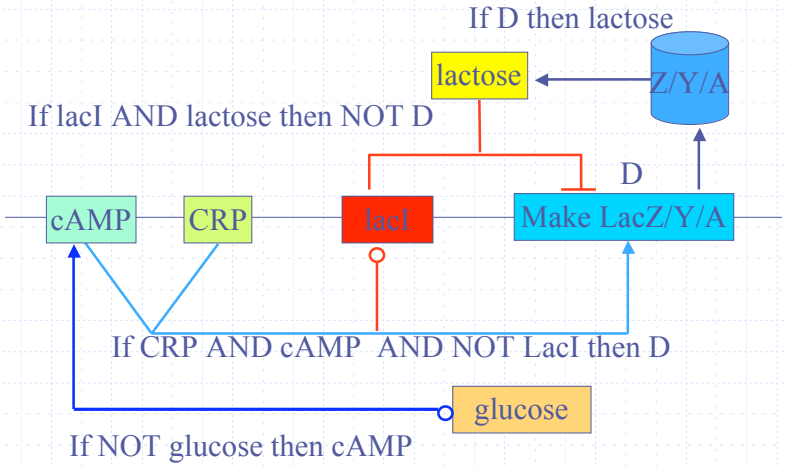
The Cell as a Regulatory Network



- Genes + signals = wires
- Transcription = gates

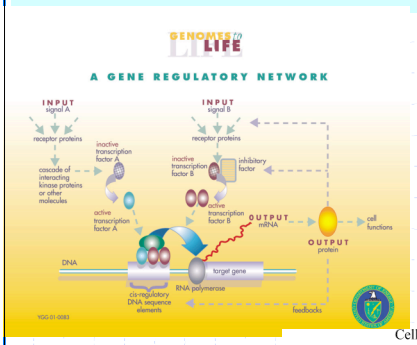
21

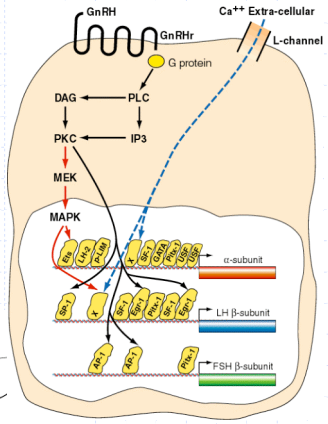
The Lac Operon Circuit



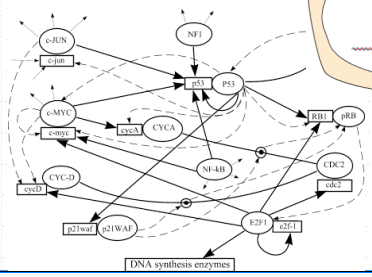
22

The Cell as a Regulatory Network





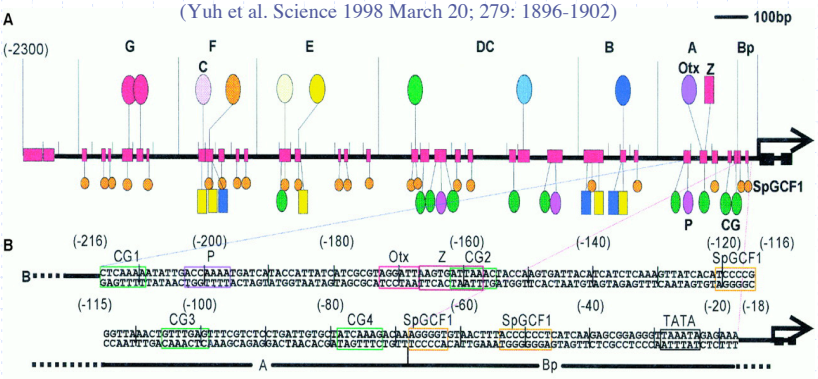
Cell cycle gene network



23

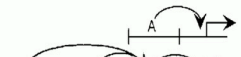
Architecture Of Cis-Regulation

(Yuh et al. Science 1998 March 20; 279: 1896-1902)



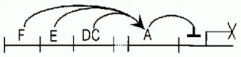
C **Module A functions:**

Vegetal plate expression in early development:

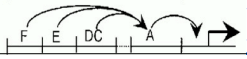


Synergism with modules B and G enhancing endoderm expression in later development:

Repression in ectoderm (modules E and F) and skeletogenic mesenchyme (module DC):



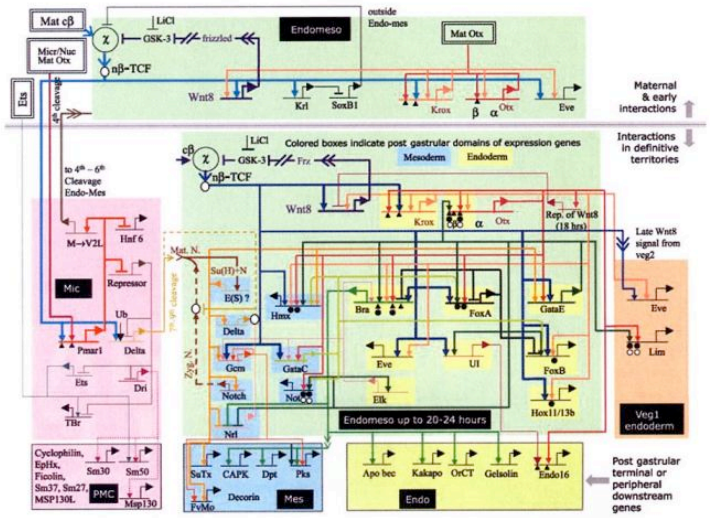
Modules E, F and DC with LiCl treatment:



24

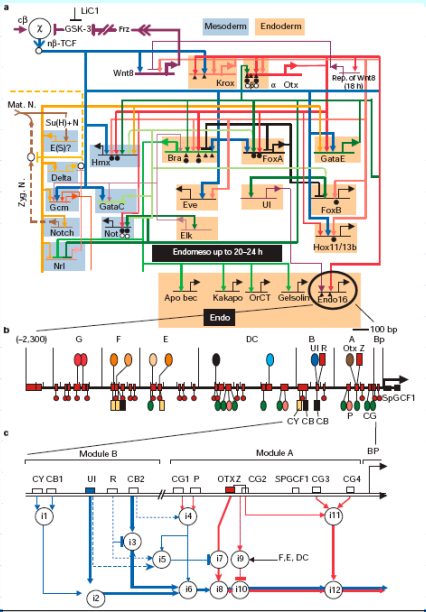
Regulatory Networks Can Be Complex

Genetic regulatory network controlling the development of the body plan of the sea urchin embryo
Davidson *et al.*, *Science*, 295(5560):1669-1678.



25

Sea-Urchin Body Structure Regulation



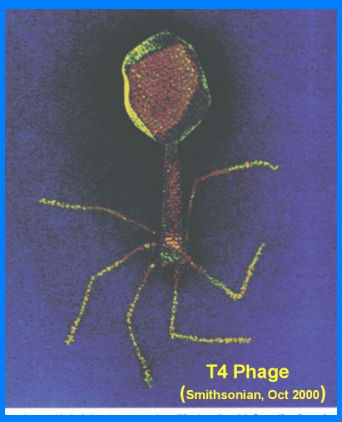
The digital code of DNA
Leroy Hood1 and David Galas
Nature, Jan 23, 2003

b, An enlargement of the promoter region of a gene, called *endo 16*, that helps modulate the development of the endoderm. It contains 34 binding sites (rectangles) for 13 different transcription factors and cofactors (illustrated as rectangles or lollipops, respectively). Six modules (A–G) of transcription factors and binding sites carry out discrete functions to developmentally regulate *endo 16*.

c, Diagram depicting the logical structures of the A and B control circuits during sea urchin development.

26

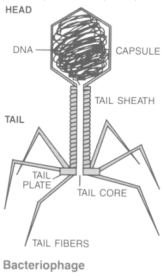
Example: the λ-phage genetic switch

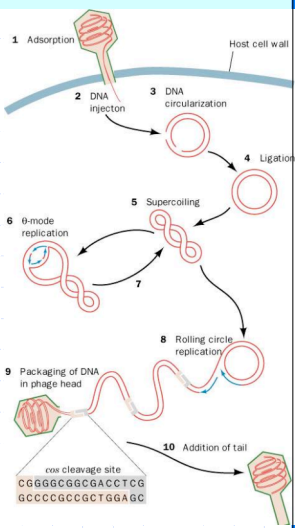


λ Phage Infects *E. coli*

- Phage injects its genome into the E-Coli
- Switches between two states:
  - **Lysogeny:** dormant duplication
  - **Lytic cycle**: rapid regeneration & lysis

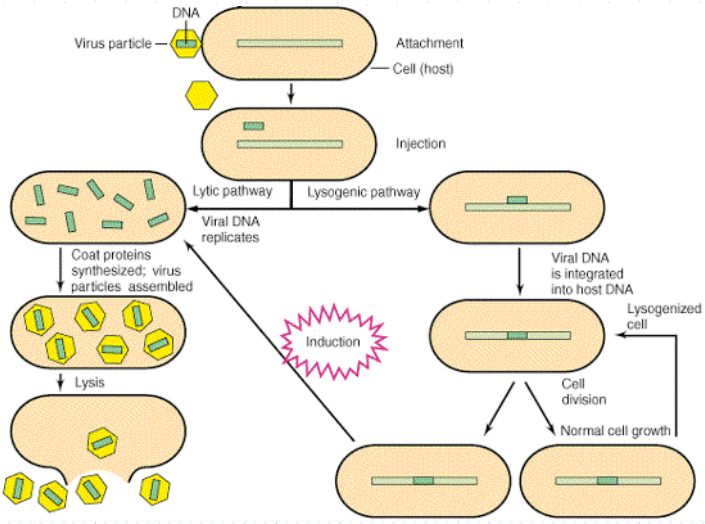
Ptashne, *A Genetic Switch*, Cell Press,1992





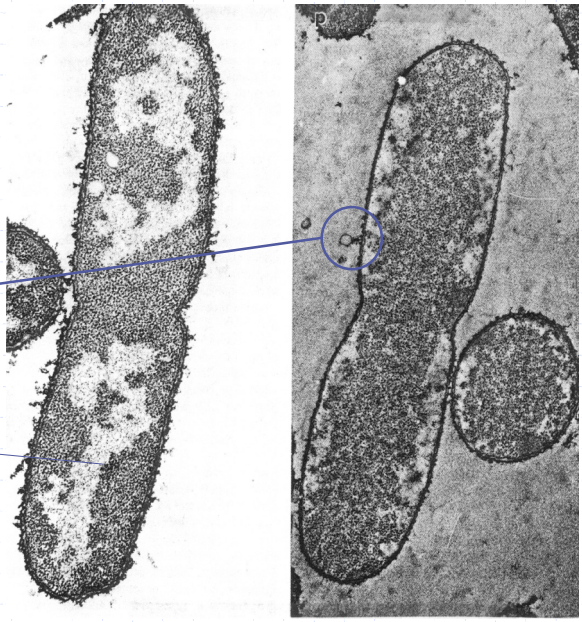
28

The Phage Is A Switch



29

Visible effects on DNA during viral infection

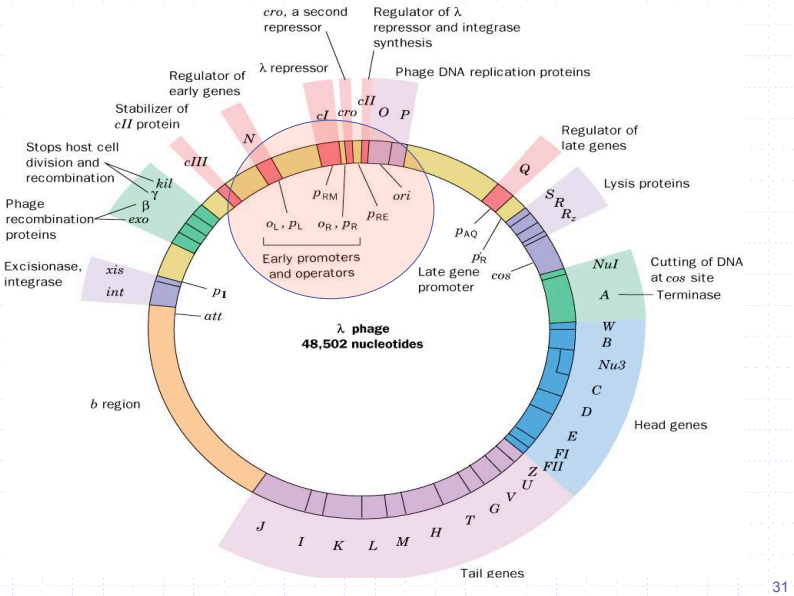


Pre-infection

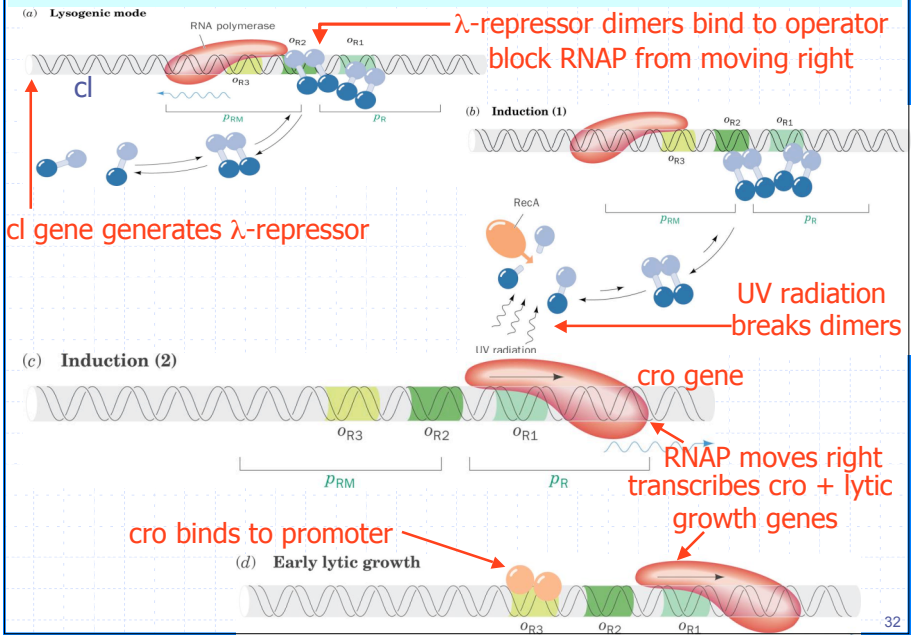
Post-infection

30

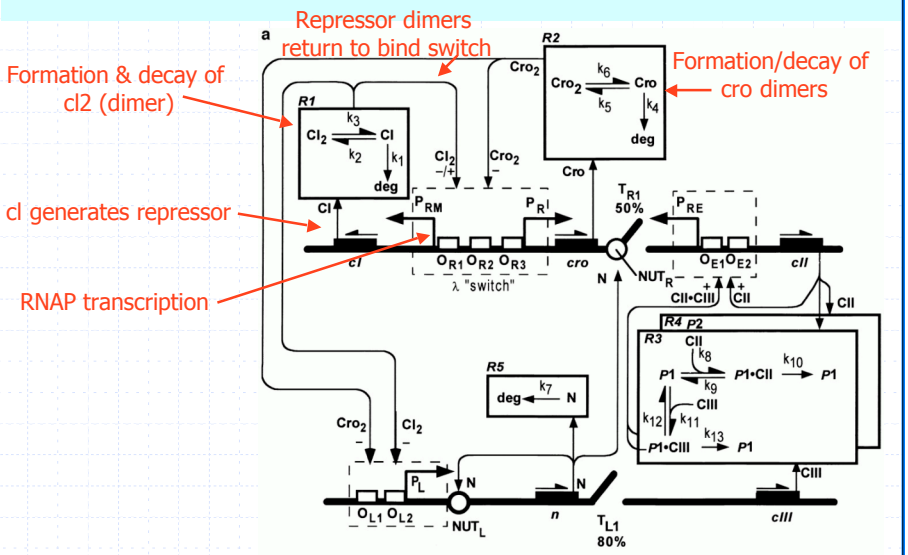
A Genetic Map



The Switch

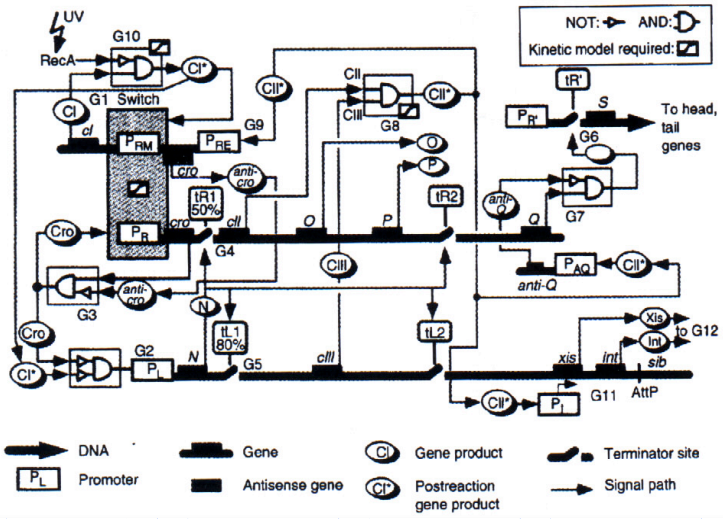


A Network Model of Lysis-Lysogeny



Arkin et al. (1998), Genetics 149(4):1633-48

Another Model



McAdams, Shapiro (1995), *Science*, 269(5524): 650-656

Key Questions

Understanding Regulation

- How to discover regulatory network pathways?
- How to discover TFs/Binding sites (motifs)?
- How to model the operations of regulatory networks?
- How to apply the models to analyze expression data?
- How does evolution change regulatory networks?

36