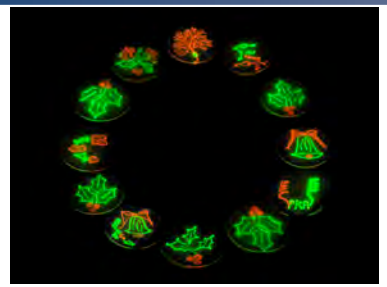
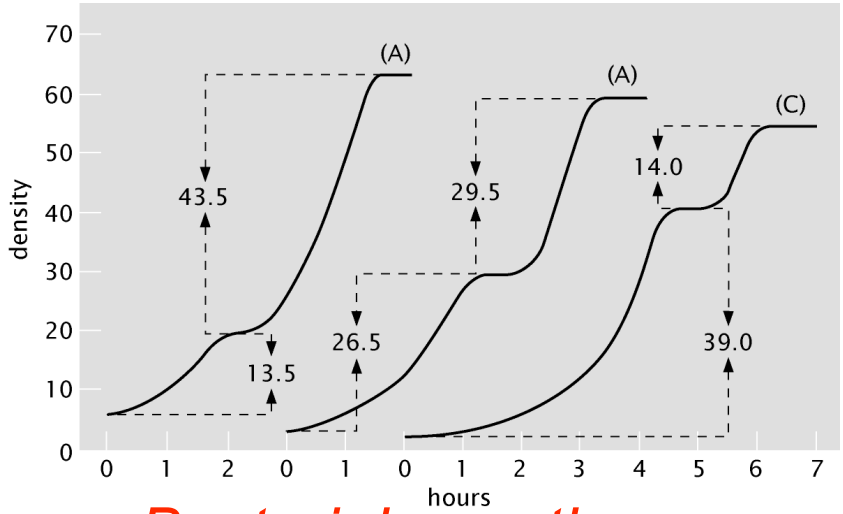
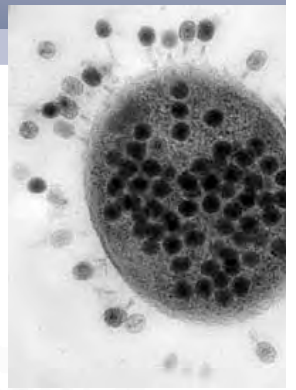
The Development of the Operon Concept: What Cells Eat and When They Die

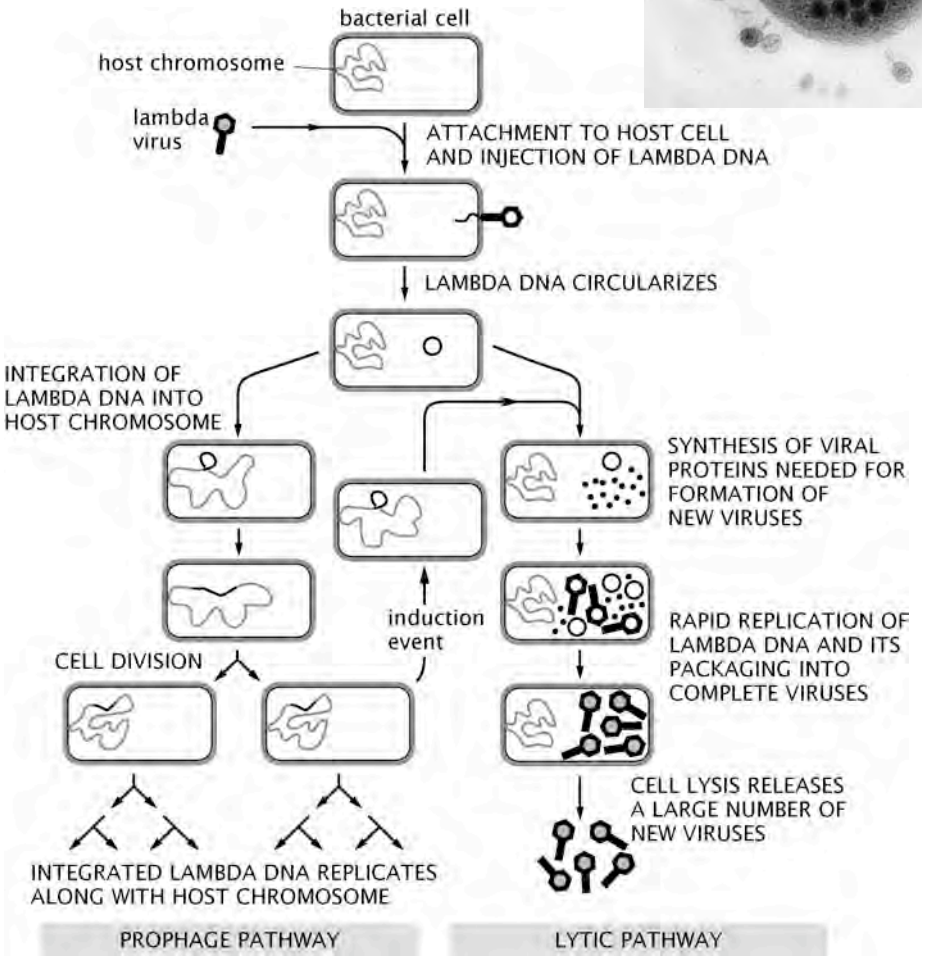




Bacterial growth curves

- ***The big idea: there are genes that control other genes!***





Exploring Regulatory Diversity

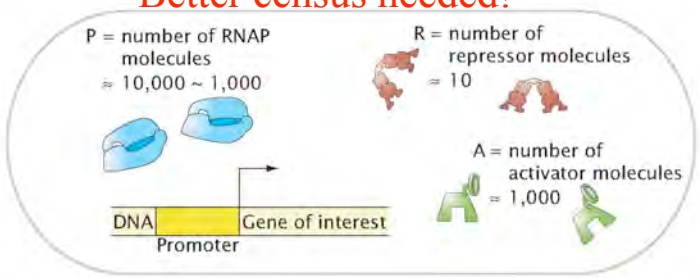
Table 1

Regulation factors for several different regulatory motifs.

Case	Regulation factor (F_{reg})	
1. Simple repressor	$(1+r)^{-1}$	$\left(1+\frac{[R]}{K_R}\right)^{-1}$
2. Simple activator	$\frac{1+ae^{-\frac{\varepsilon_{ap}}{k_BT}}}{1+a}$	$\frac{1+\frac{[A]}{K_A}f}{1+\frac{[A]}{K_A}}$
3. Activator recruited by a helper (*H*)	$\frac{1+a\frac{1+he^{-\frac{\varepsilon_{hd}}{k_BT}}}{1+h}e^{-\frac{\varepsilon_{ap}}{k_BT}}}{1+a\frac{1+he^{-\frac{\varepsilon_{hp}}{k_BT}}}{1+h}}$	$\frac{1+\frac{[H]}{K_H}+\frac{[A]}{K_A}f+\frac{[A][H]}{K_AK_H}f_{\omega}}{1+\frac{[H]}{K_H}+\frac{[A]}{K_A}+\frac{[A][H]}{K_AK_H}\omega}$
4. Repressor recruited by a helper (*H*)	$\left(1+\frac{1+he^{-\frac{\varepsilon_{hr}}{k_BT}}}{1+h}r\right)^{-1}$	$\frac{1+\frac{[H]}{K_H}}{1+\frac{[H]}{K_H}+\frac{[R]}{K_R}+\frac{[R][H]}{K_RK_H}\omega}$
5. Dual repressors	$(1+r_1)^{-1}(1+r_2)^{-1}$	$\left(1+\frac{[R_1]}{K_{R_1}}\right)^{-1}\left(1+\frac{[R_2]}{K_{R_2}}\right)^{-1}$
6. Dual repressors interacting	$\left(1+r_1+r_2+r_1r_2e^{-\frac{\varepsilon_{r_1r_2}}{k_BT}}\right)^{-1}$	$\left(1+\frac{[R_1]}{K_{R_1}}+\frac{[R_2]}{K_{R_2}}+\frac{[R_1][R_2]}{K_{R_1}K_{R_2}}\omega\right)^{-1}$
7. Dual activators interacting	$\frac{1+a_1e^{-\frac{\varepsilon_{a_1p}}{k_BT}}+a_2e^{-\frac{\varepsilon_{a_2p}}{k_BT}}+a_1a_2e^{-\frac{\varepsilon_{a_1p}+\varepsilon_{a_2p}+\varepsilon_{a_1a_2}}{k_BT}}}{1+a_1+a_2+a_1a_2e^{-\frac{\varepsilon_{a_1p}+\varepsilon_{a_2p}}{k_BT}}}$	$\frac{1+\frac{[A_1]}{K_{A_1}}f_1+\frac{[A_2]}{K_{A_2}}f_2+\frac{[A_1][A_2]}{K_{A_1}K_{A_2}}f_1f_2\omega}{1+\frac{[A_1]}{K_{A_1}}+\frac{[A_2]}{K_{A_2}}+\frac{[A_1][A_2]}{K_{A_1}K_{A_2}}\omega}$
8. Dual activators cooperating via looping	$\frac{1+a_1e^{-\frac{\varepsilon_{a_1p}}{k_BT}}+a_2e^{-\frac{\varepsilon_{a_2p}}{k_BT}}+a_1a_2e^{-\frac{\varepsilon_{a_1p}+\varepsilon_{a_2p}+F_{loop}}{k_BT}}}{(1+a_1)(1+a_2)}$	$\frac{1+\frac{[A_1]}{K_{A_1}}f_1+\frac{[A_2]}{K_{A_2}}f_2+\frac{[A_1]}{K_{A_1}}\frac{[A_2]}{K_{A_2}}f_1f_2\omega}{\left(1+\frac{[A_2]}{K_{A_2}}\right)\left(1+\frac{[A_1]}{K_{A_1}}\right)}$
9. Repre		
10. *N* no		

Regulati… symbol … in terms … regulatio… TF we in… the conc… the DNA…

Better census needed!



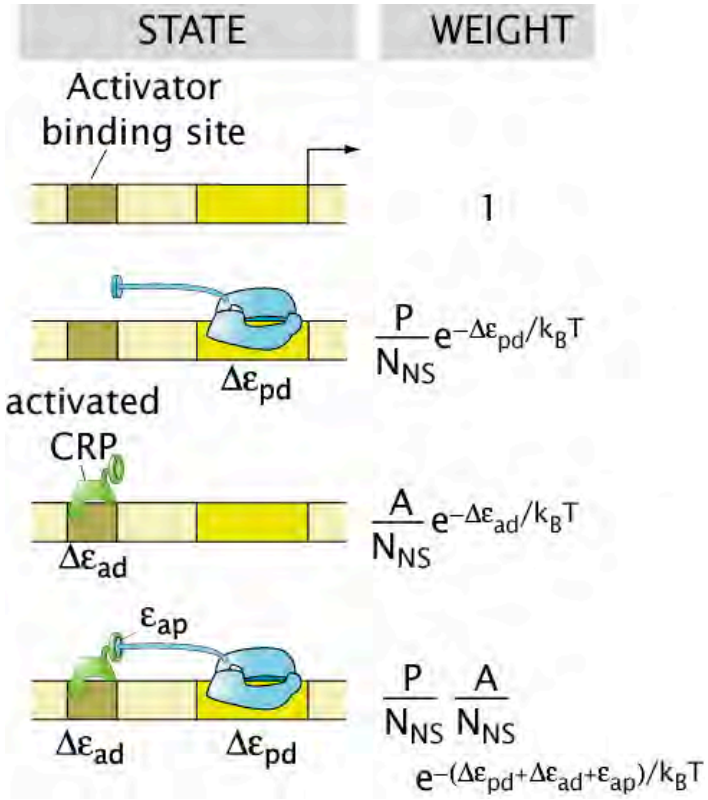
Key point: We can work ou… the regulation factor for ma… other scenarios including other looping scenarios.

STATE	WEIGHT
	1
	$\frac{P}{N_{ns}}\,e^{-\Delta\varepsilon_{pd}}$
	$\frac{A}{N_{ns}}\,e^{-\Delta\varepsilon_{a_1d}}$
	$\frac{A}{N_{ns}}\,e^{-\Delta\varepsilon_{a_2d}}$
	$\frac{A}{N_{ns}}\frac{A}{N_{ns}}\,e^{-(\Delta\varepsilon_{a_1d}+\Delta\varepsilon_{a_2d})}$
	$\frac{P}{N_{ns}}\frac{A}{N_{ns}}\,e^{-(\Delta\varepsilon_{pd}+\Delta\varepsilon_{a_1d}+\varepsilon_{a_1p})}$
	$\frac{P}{N_{ns}}\frac{A}{N_{ns}}\,e^{-(\Delta\varepsilon_{pd}+\Delta\varepsilon_{a_2d}+\Delta\varepsilon_{a_2p})}$
	$\frac{P}{N_{ns}}\frac{A}{N_{ns}}\frac{A}{N_{ns}}\,e^{-(\Delta\varepsilon_{pd}+\Delta\varepsilon_{a_1d}+\Delta\varepsilon_{a_2d}+\varepsilon_{a_1p}+\varepsilon_{a_2p}+F_{loop})}$

Synergistic Activation

How Should We Think About Regulation Quantitatively?

"Thermodynamic Models" – Equilibrium Notions



Rate Equation Perspecti

$$\frac{d[mRNA_{Rep}]}{dt} = V_{mRNA-Rep} - (k_{d,mRNA-Rep} + \mu)\cdot[mRNA_{Rep}]$$

$$\frac{d[Rep]}{dt} = V_{Rep} - (k_{d,Rep} + \mu)\cdot[Rep]$$

$$\frac{d[mRNA_{ZYA}]}{dt} = V_{mRNA-ZYA} - (k_{d,mRNA-ZYA} + \mu)\cdot[mRNA_{ZYA}]$$

$$\frac{d[\beta gal]}{dt} = V_{\beta gal} - (k_d + \mu)\cdot[\beta gal]$$

$$\frac{d[Perm]}{dt} = V_{Perm} - (k_d + \mu)\cdot[Perm]$$

$$\frac{d[Lac_{in}]}{dt} = V_{t,Lac} - V_{cat,Lac} - V_{Lac-Allo} - \mu\cdot[Lac_{in}]$$

$$\frac{d[Allo]}{dt} = V_{Lac-Allo} - V_{cat,Allo} - \mu\cdot[Allo]$$

$$\frac{d[cAMP]}{dt} = V_{cAMP} - (k_{ex} + \mu)\cdot[cAMP]$$

$$\frac{d[Glu_{ext}]}{dt} = (V_{out,Glu} - V_{t,Glu})\cdot X$$

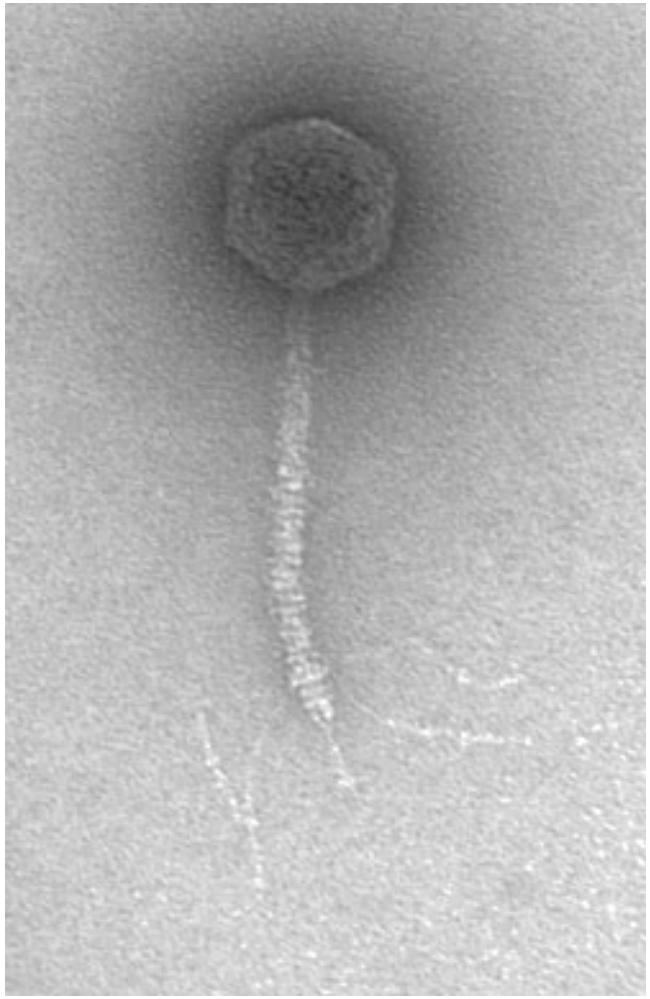
$$\frac{d[Lac_{ext}]}{dt} = -V_{t,Lac}\cdot X$$

$$\frac{dX}{dt} = \mu X$$

$$\frac{d[Glu6P]}{dt} = V_{t,Glu} + 2\cdot(V_{cat,Lac} + V_{cat,Allo}) - \frac{\mu}{Y_{X/Glu6P}} - \mu\cdot[Glu6P]$$

Wong, Gladney, and Keasling

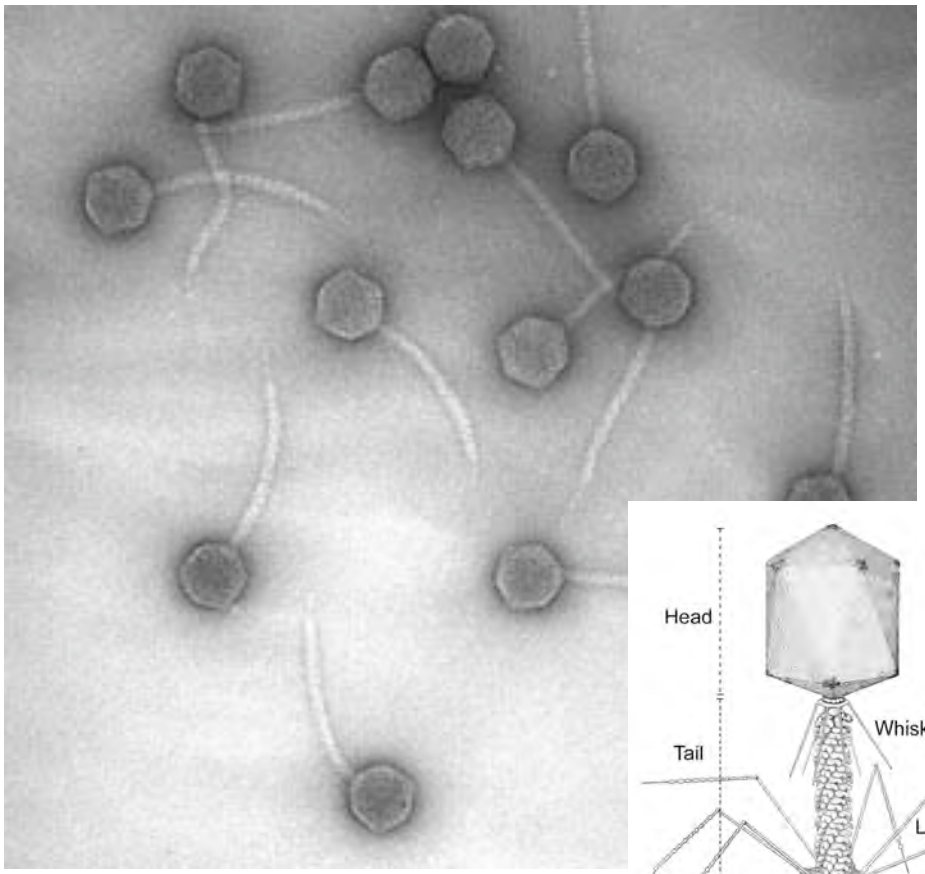
The Lambda Switch: The Other Hydrogen Atom of Gene Regulation

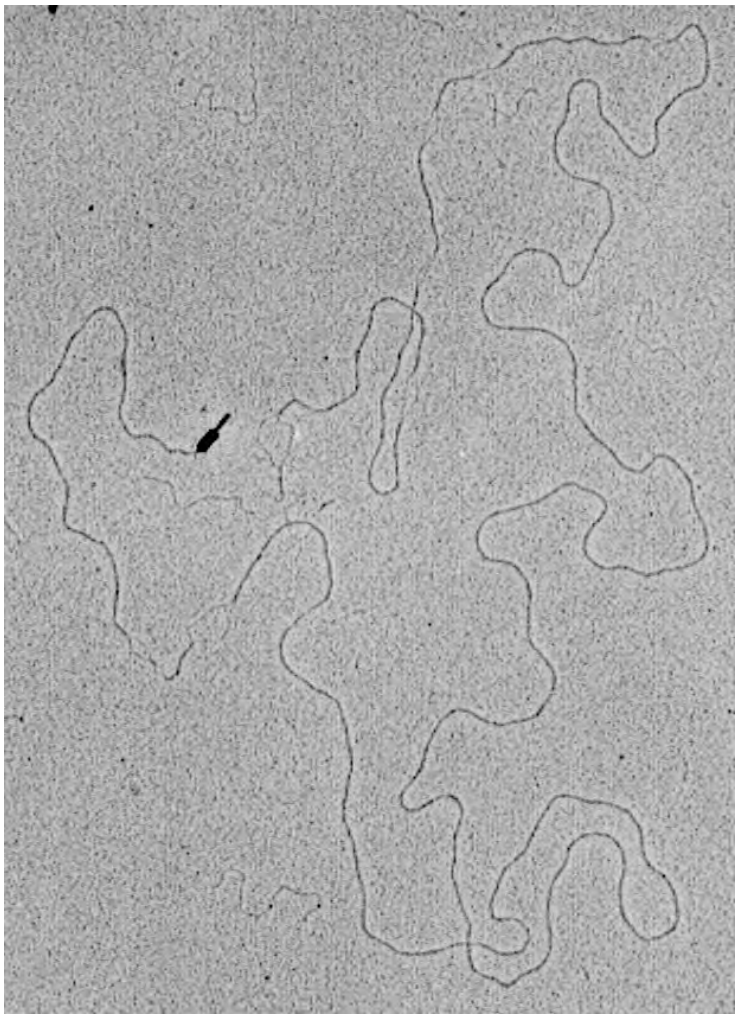


Roger Hendrix

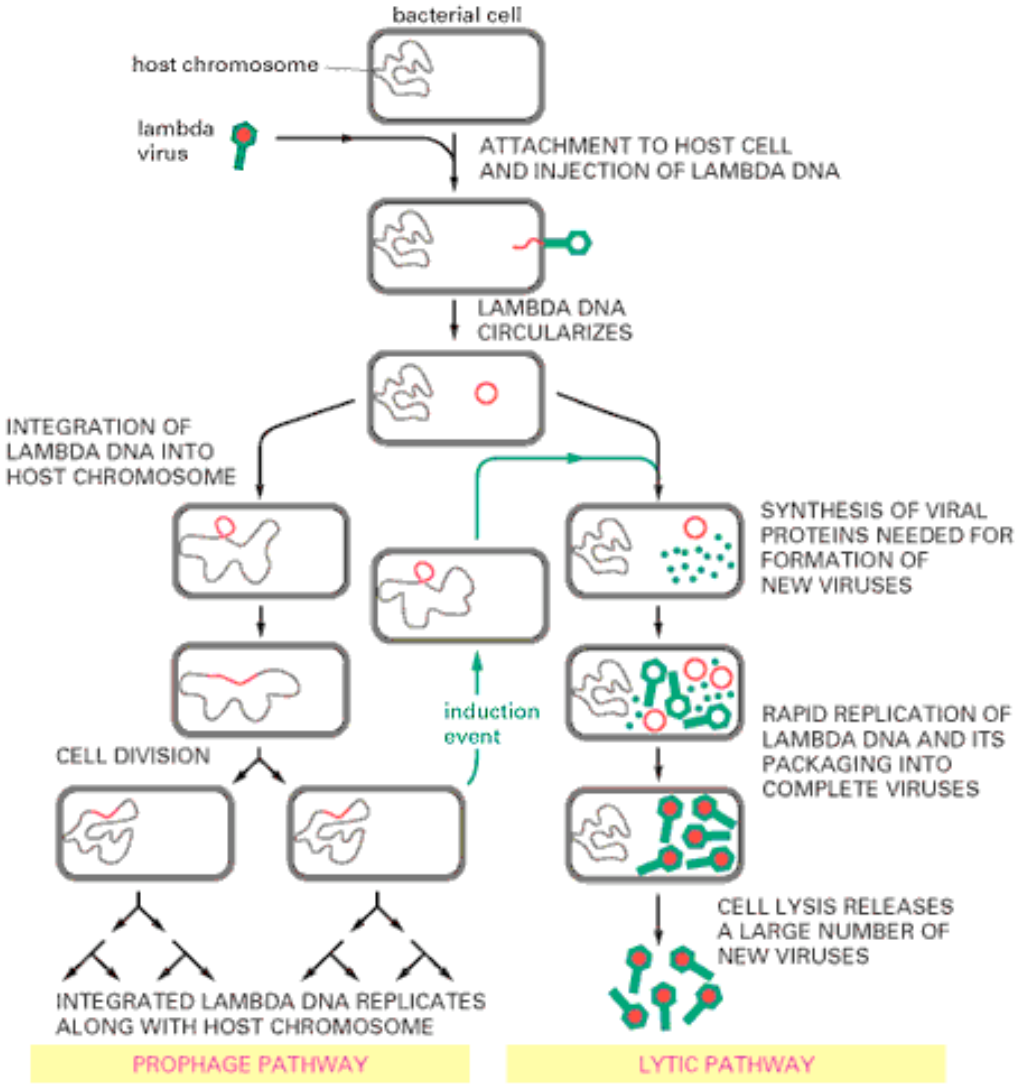
Bacteriophage and Their Genomes

http://www.biochem.wisc.edu/inman/empics/0020b.j

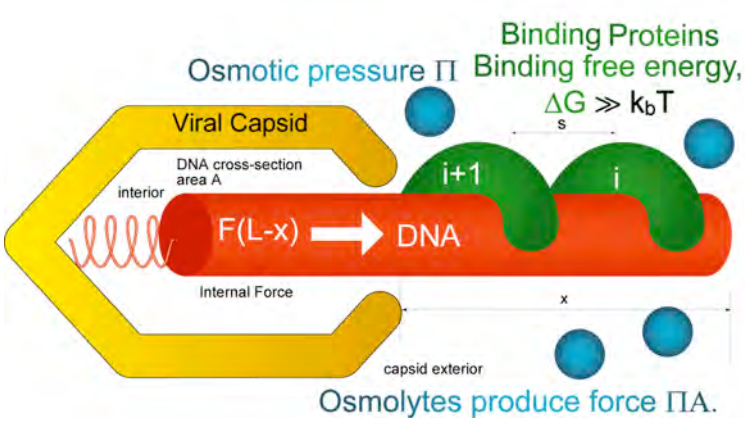




The Life Cycle of Bacteriophage Lambda

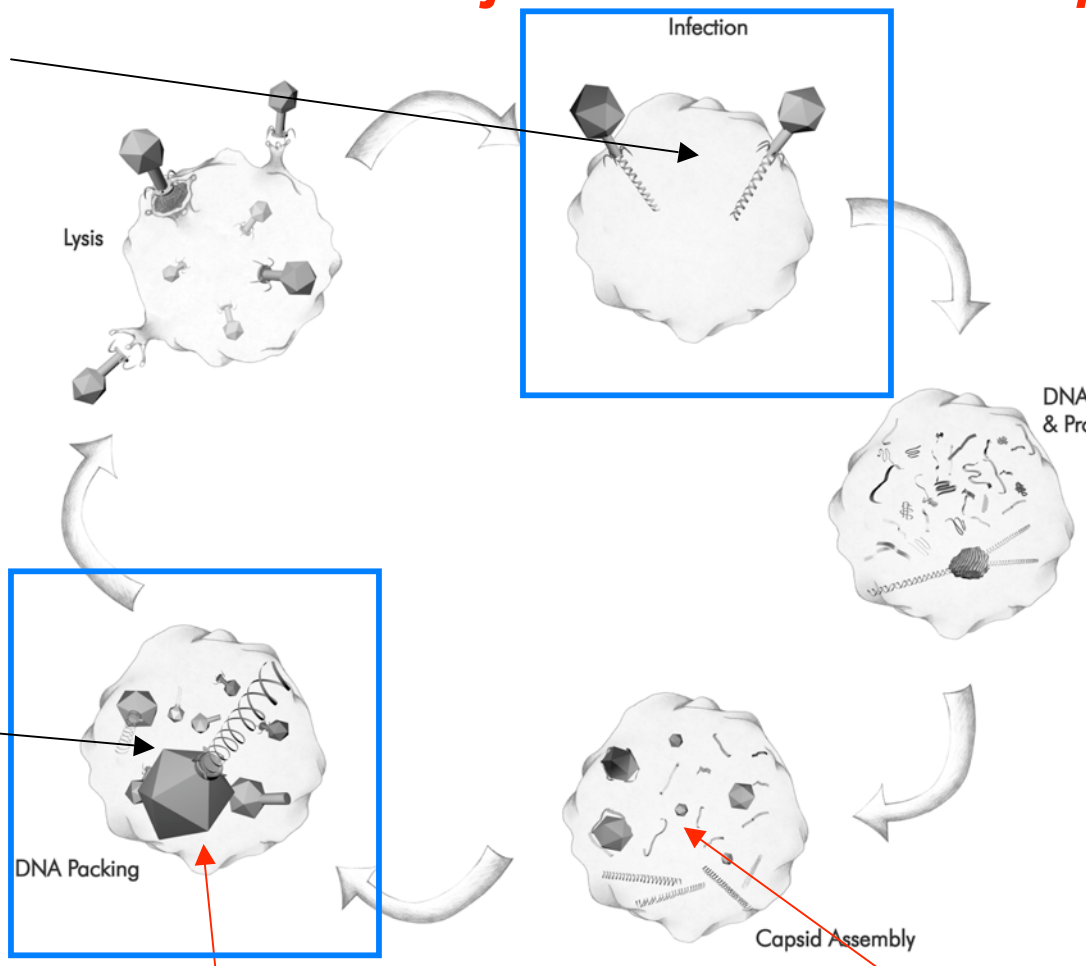


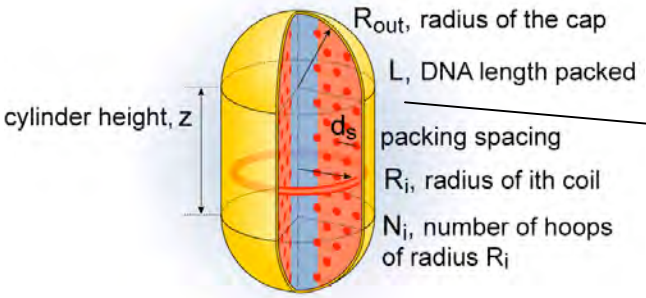
Physical Consequences of the Tight Squeeze in the Life Cycle of a Bacteriophage



Forceful ejection

Rate of ejection: ≈ 100 - 1000b





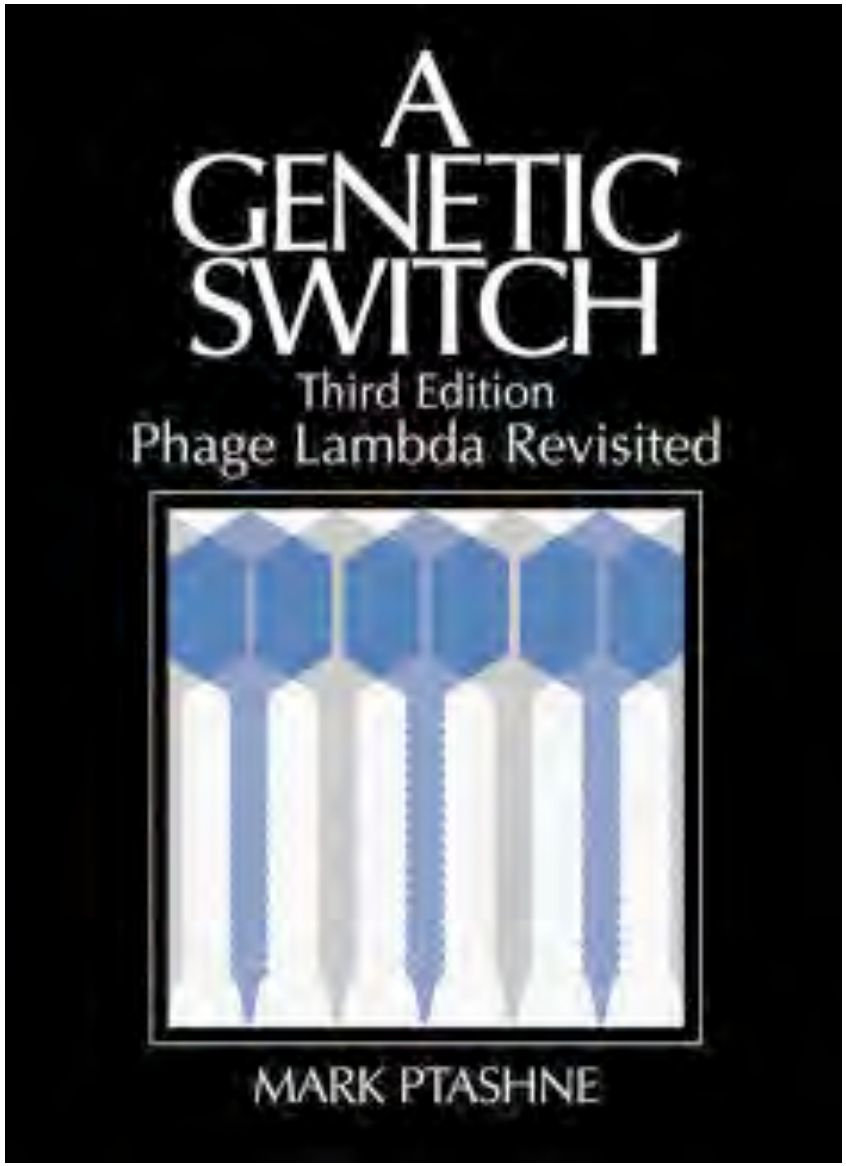
Construct a physical model of these processes.

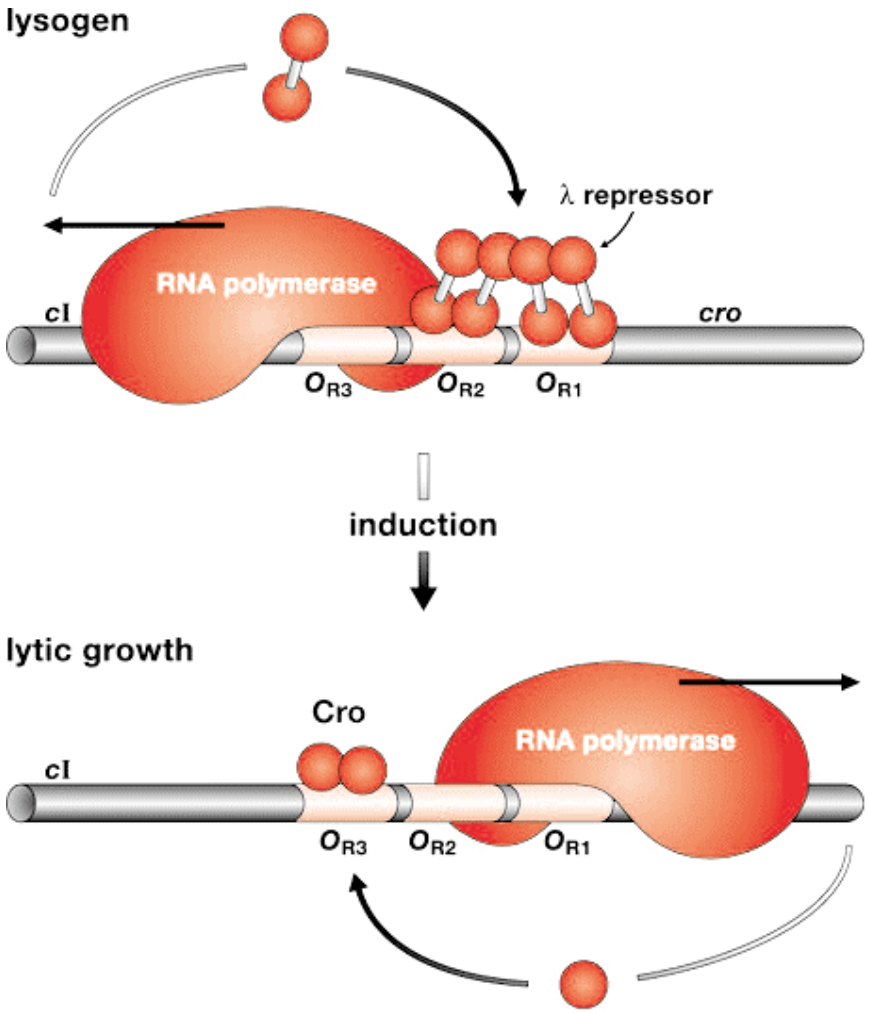
Rate of packing: 100bp/sec

"Some assembly required"

Self-assem

A Genetic Switch





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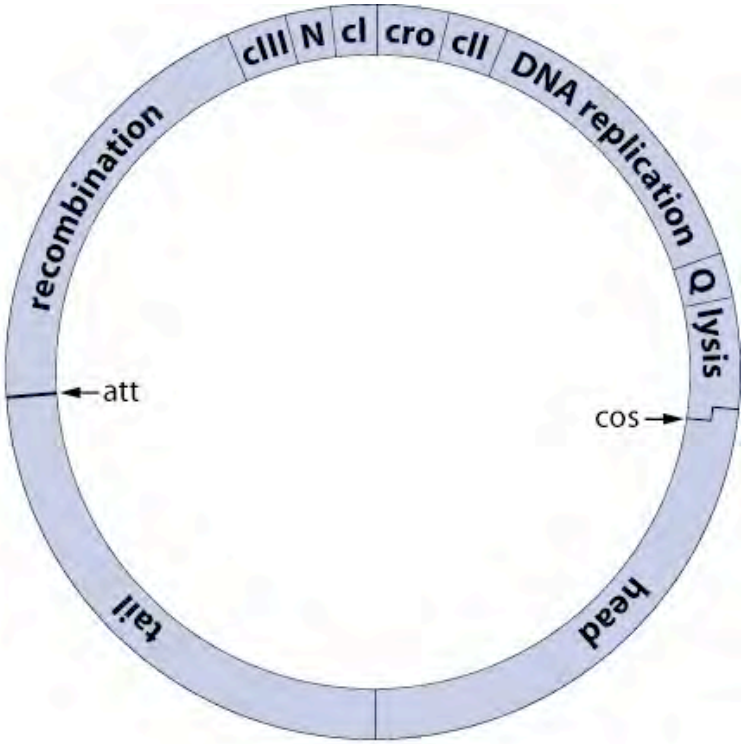
The Lambda Genome



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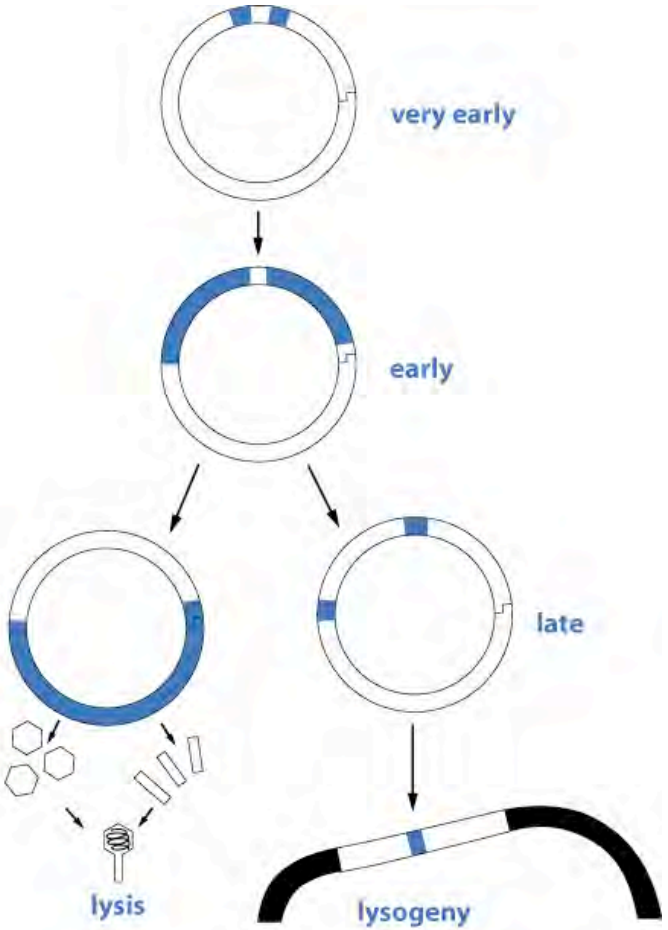
Chapter 3, Figure 1



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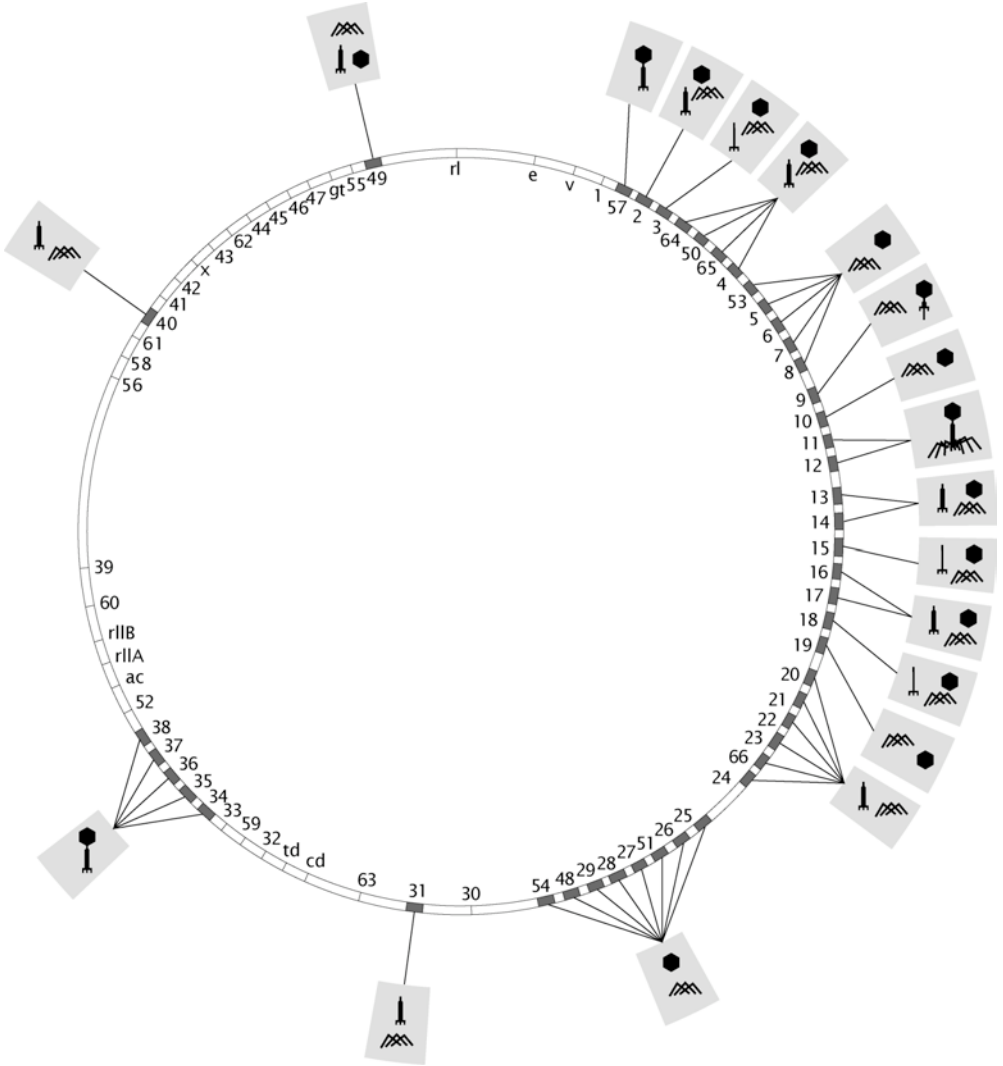
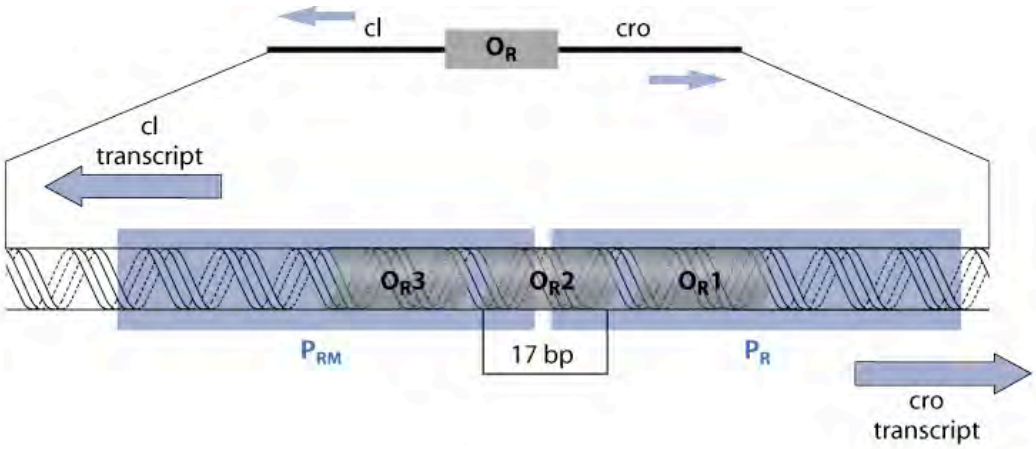
Chapter 3, Figure 3

A More Detailed Example of the Parrts List



The Lambda Switch: Lysogenic State



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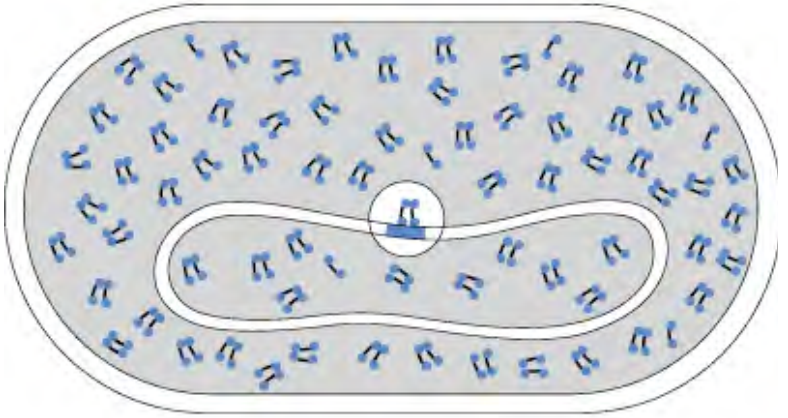

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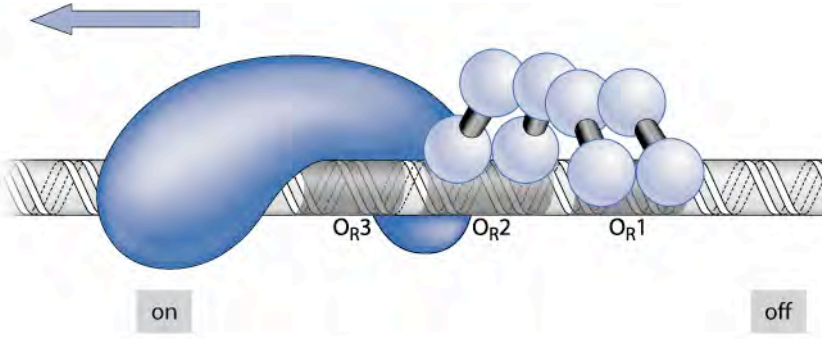

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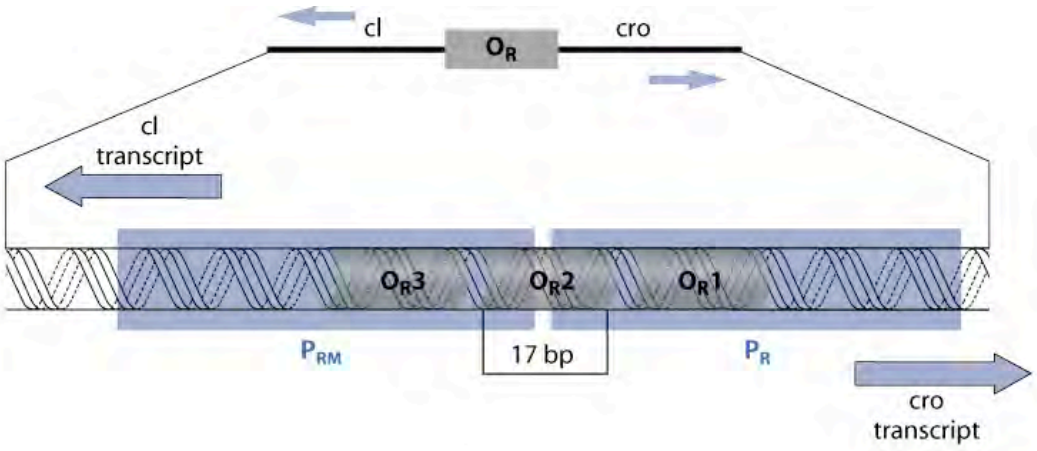
Chapter 1, Figure 19

The Lambda Switch: Lytic State



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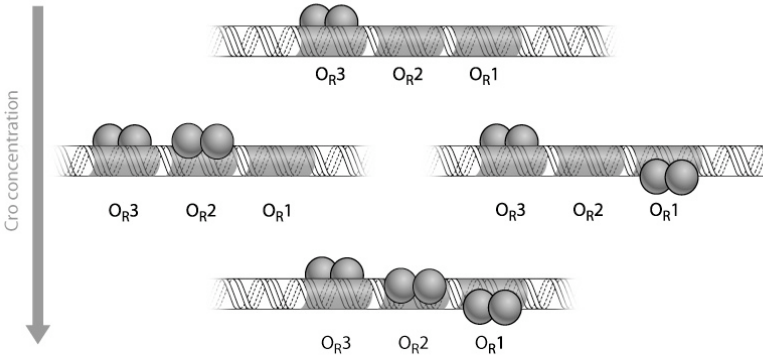

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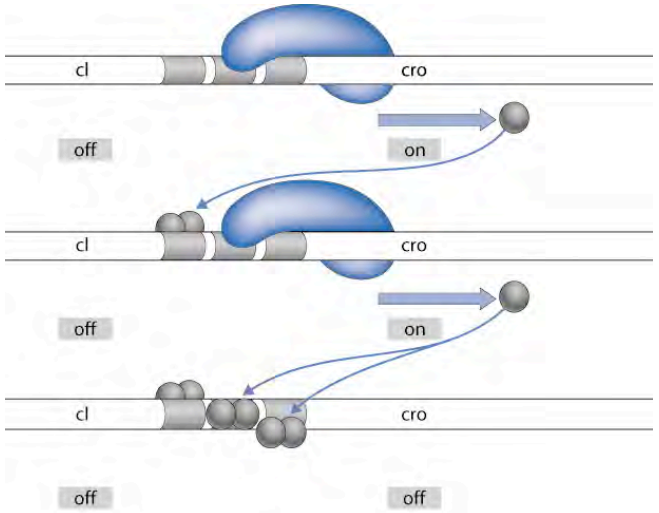

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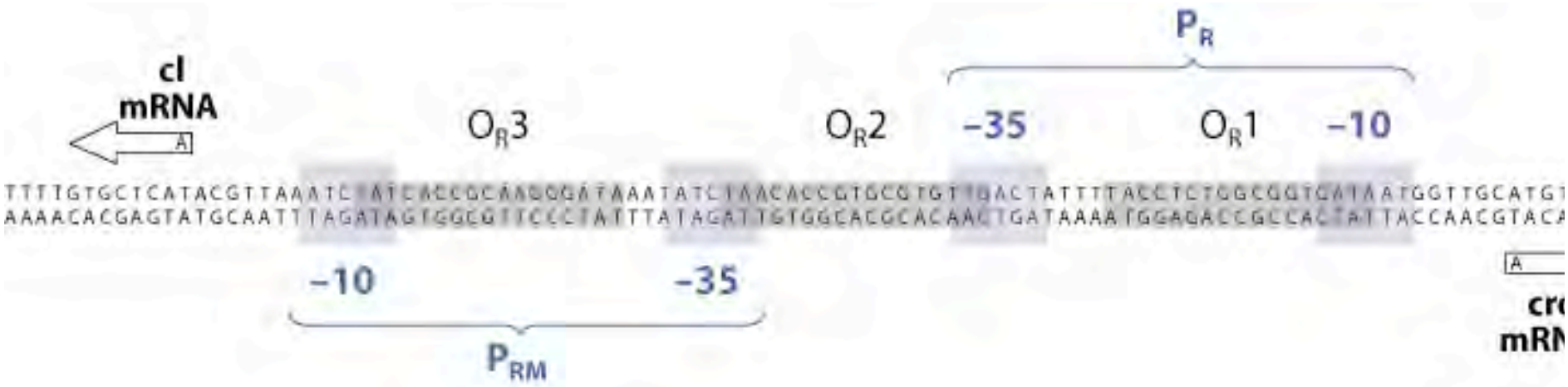
Chapter 1, Figure 24

DNA Geography of the Switch



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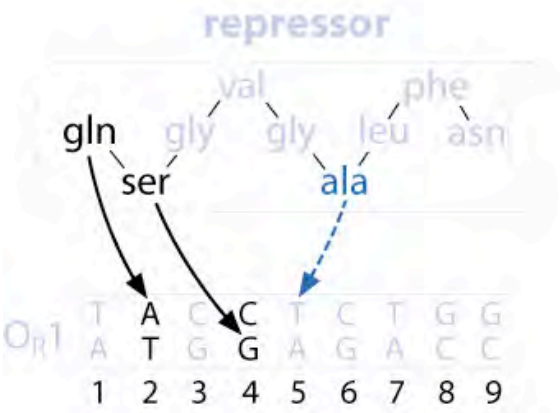
Chapter 2, Figure 16

Binding of Transcription Factors



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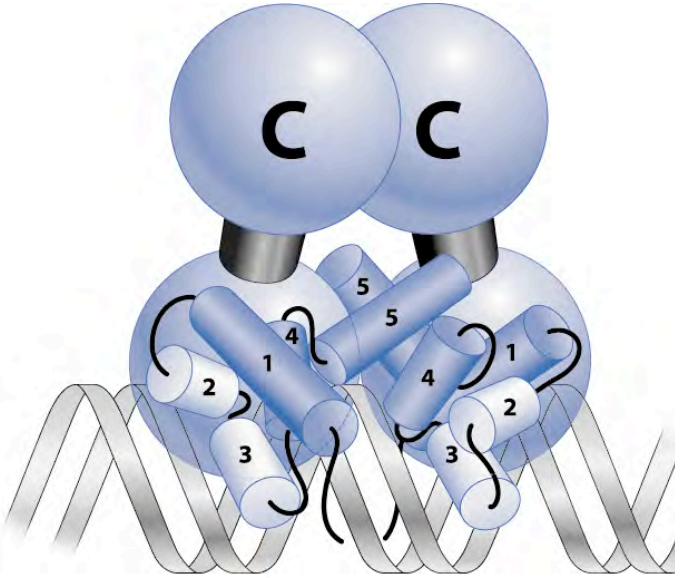
Chapter 2, Figure 11a



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Chapter 2, Figure 6

Synthetic Genetic Switch

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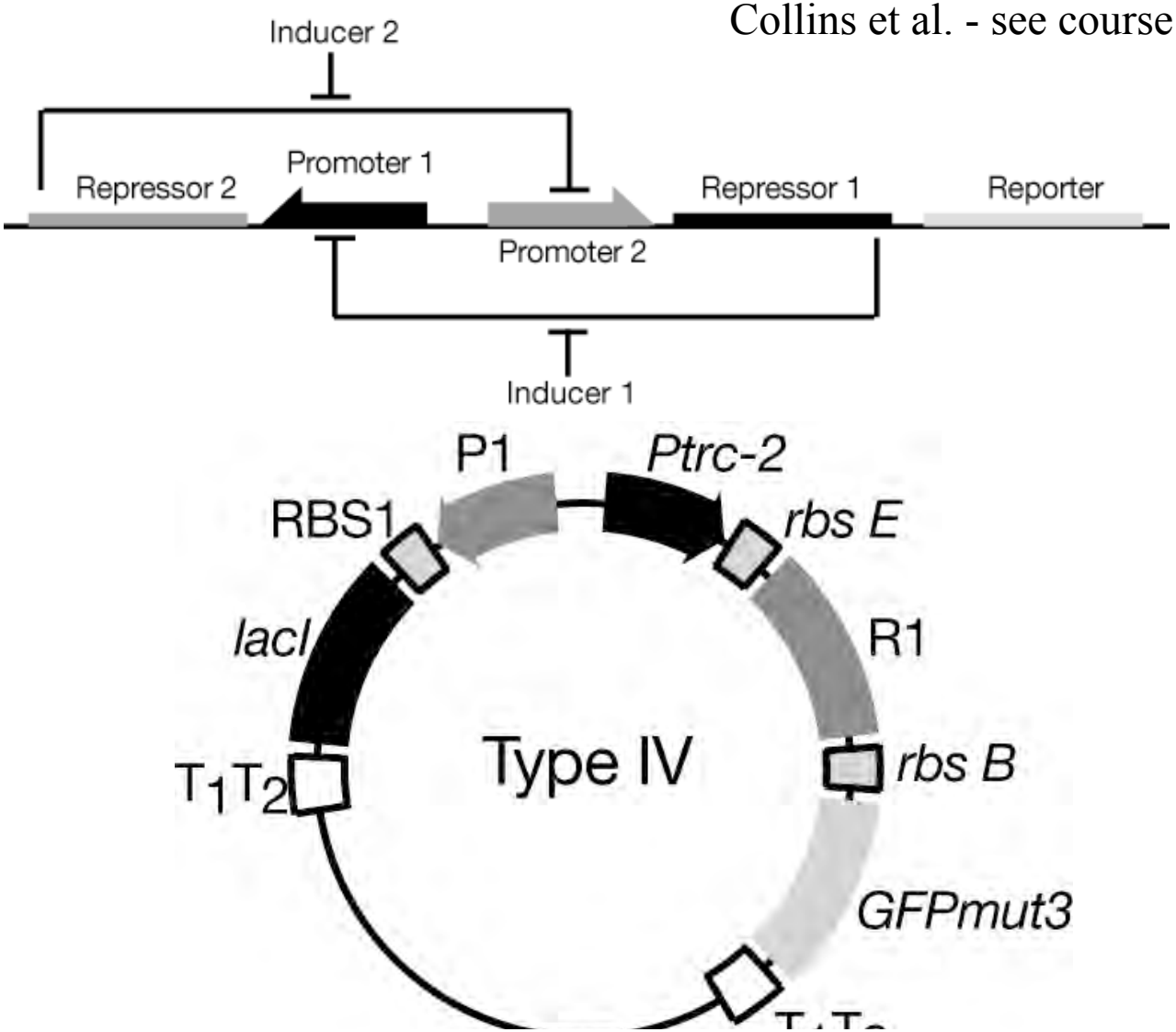
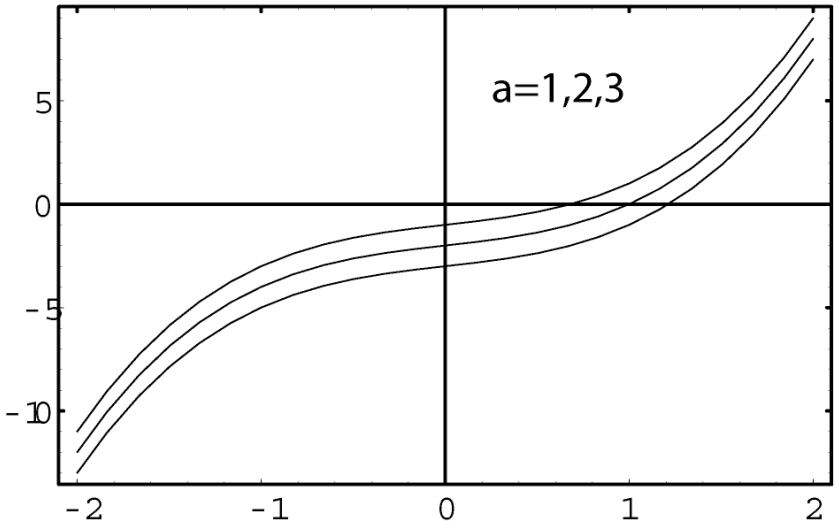


Stable Solutions

a)



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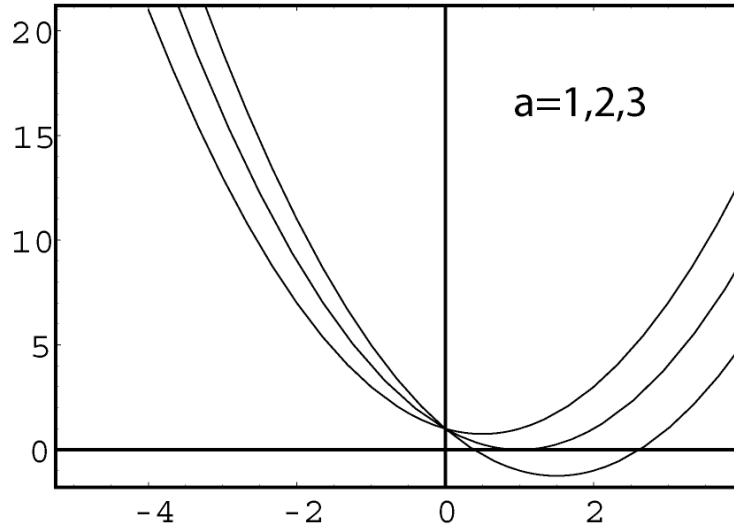
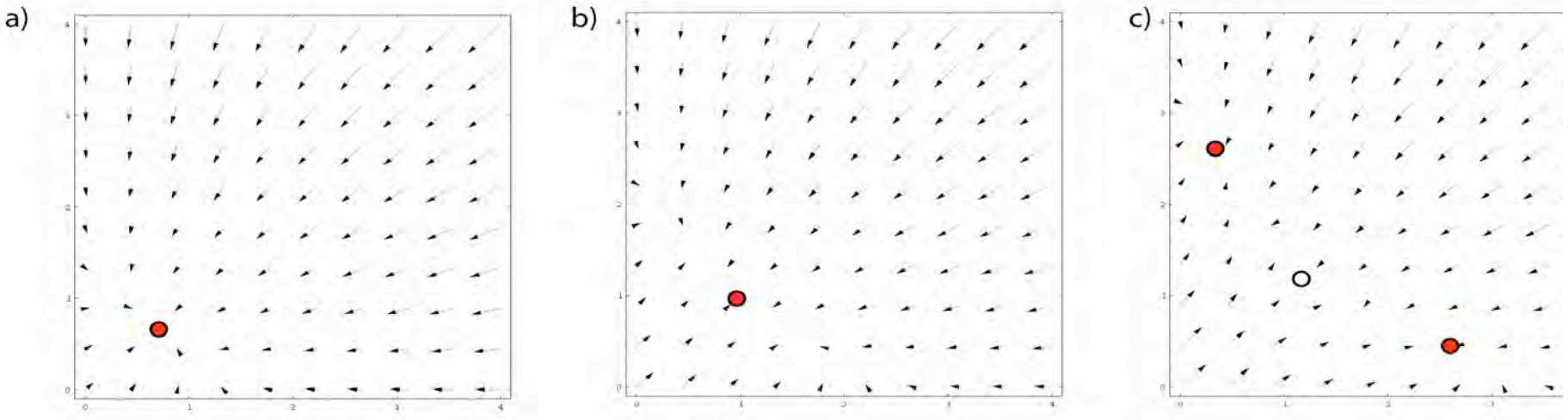


Phase Portrait for the Switch



Synthetic Genetic Switch

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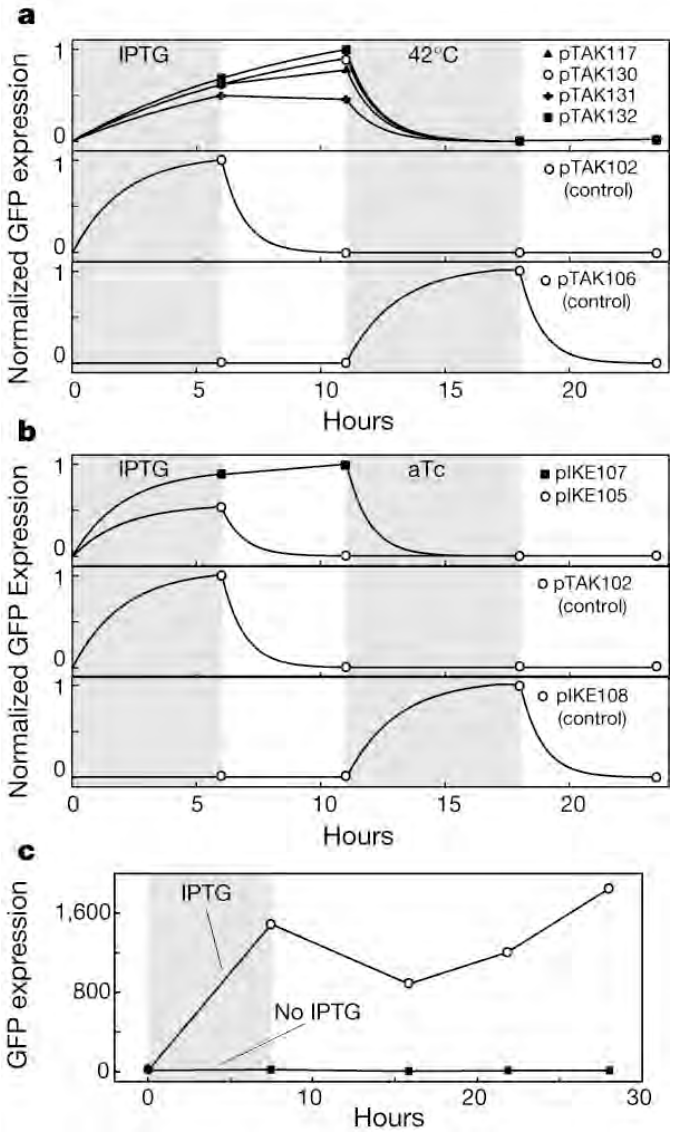

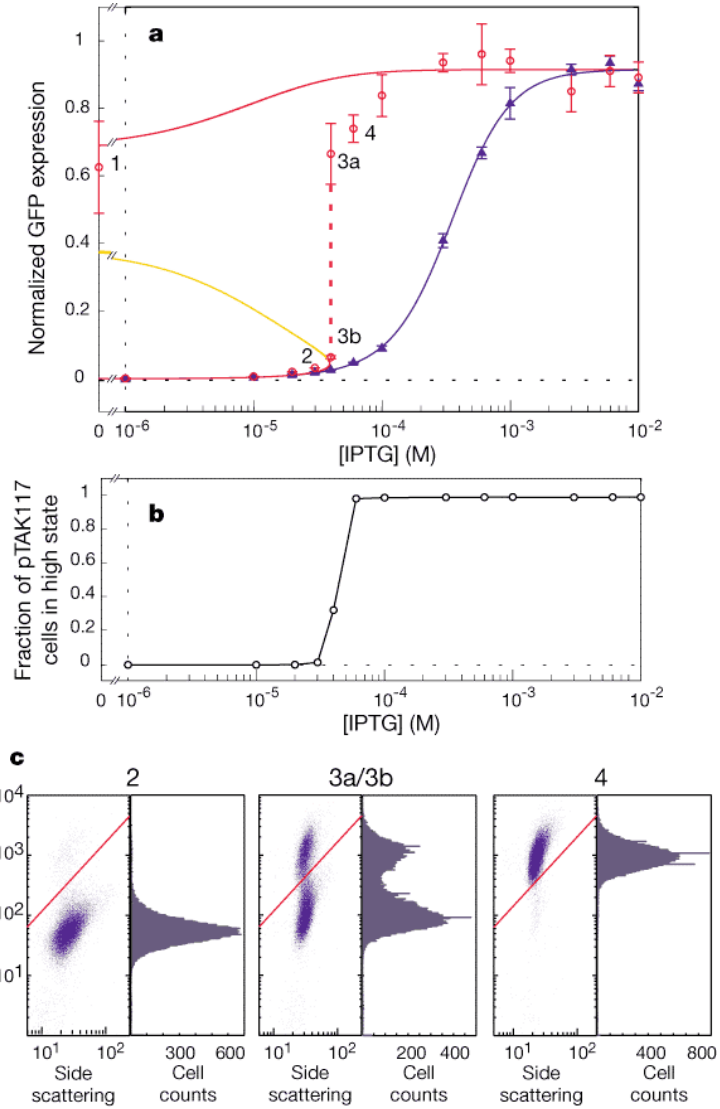

Coupling of Genes in Networks