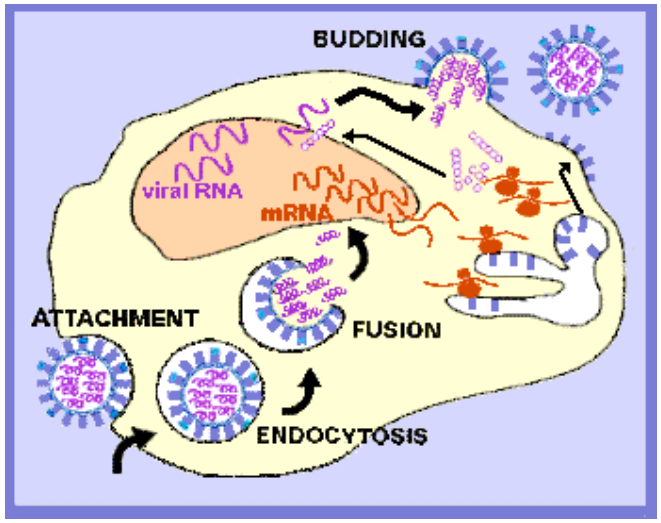
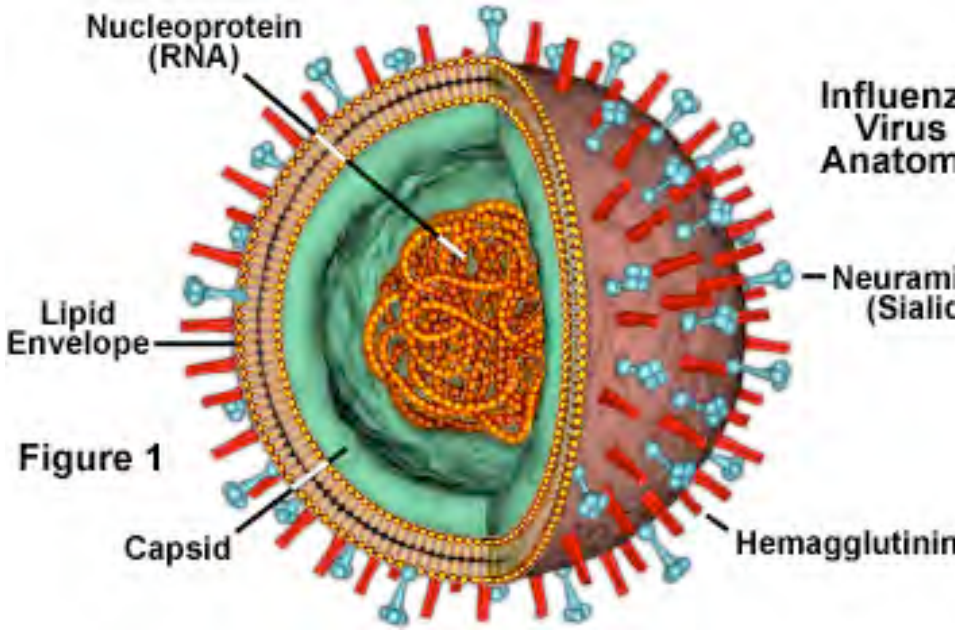
Homework 2 comments

http://web.uct.ac.za/depts/mmi/jmoodie/flu2life.gif





http://micro.magnet.fsu.edu/cells/viruses/influenzavirus

Homework 2 comments

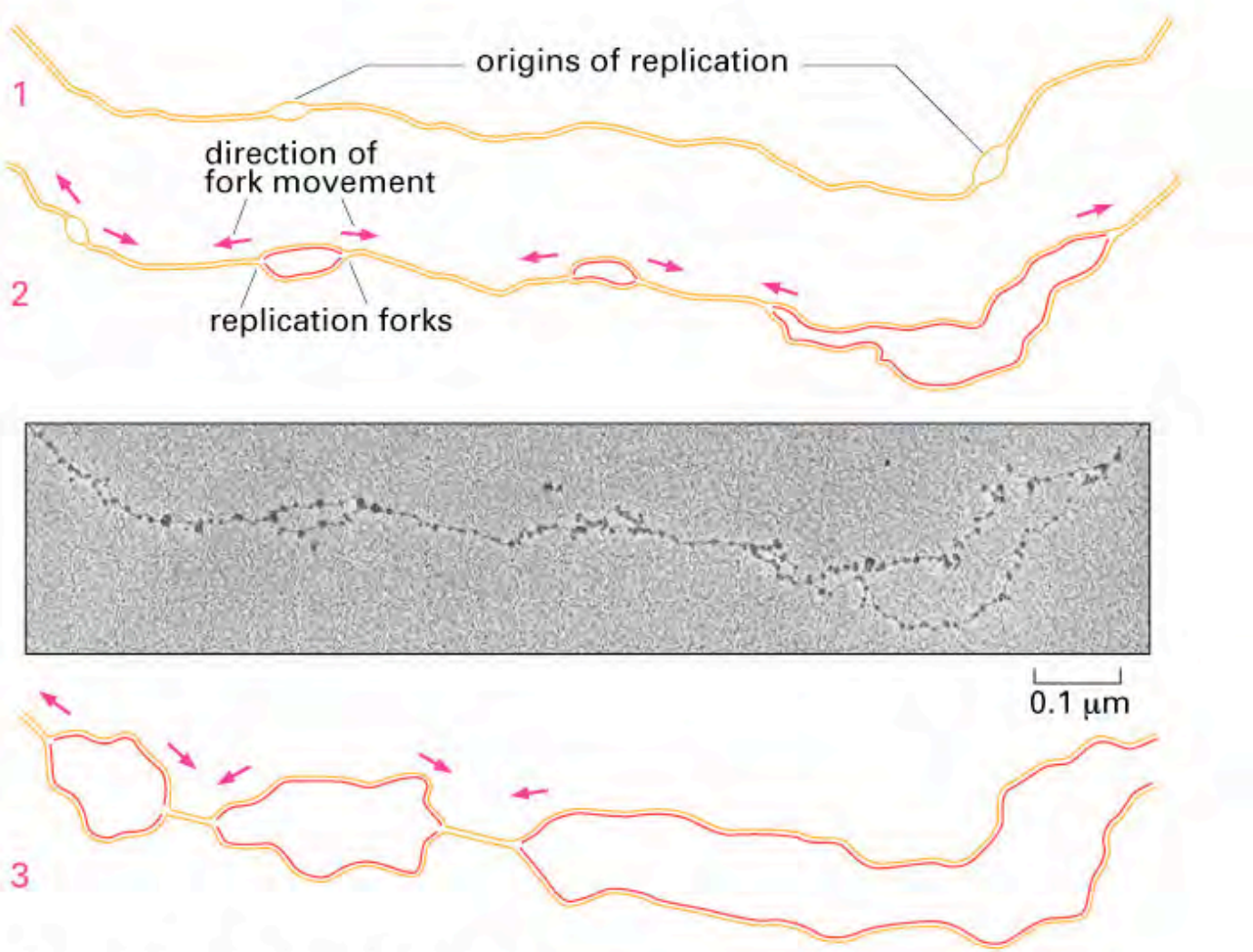
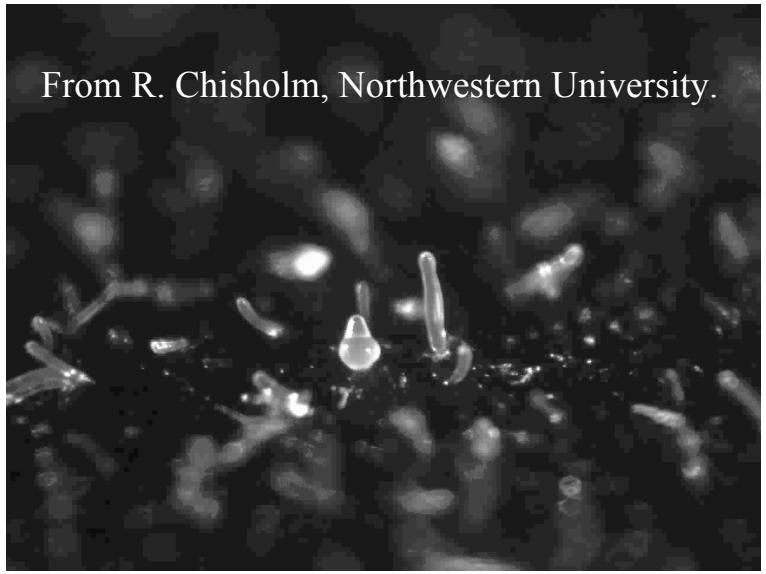
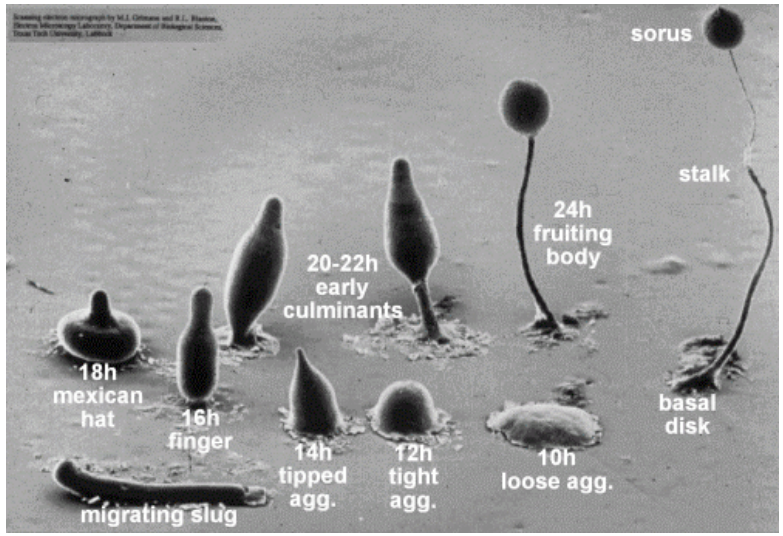


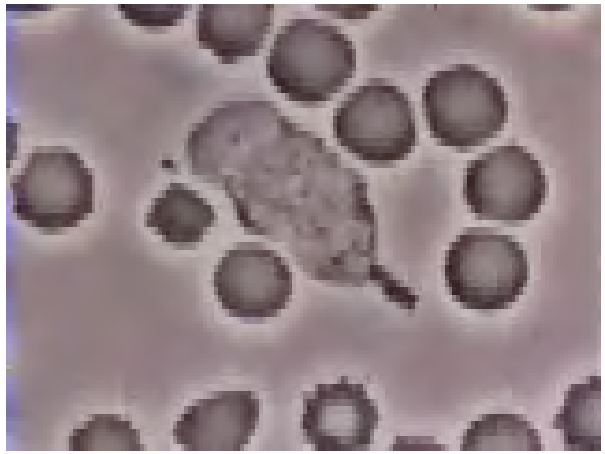
Figure 6-9 Essential Cell Biology, 2/e. (© 2004 Garland Science)

How Cells Decide Where to Go, What to Eat and Wha to Become: The Physics of Signaling and Regulation





David Rogers



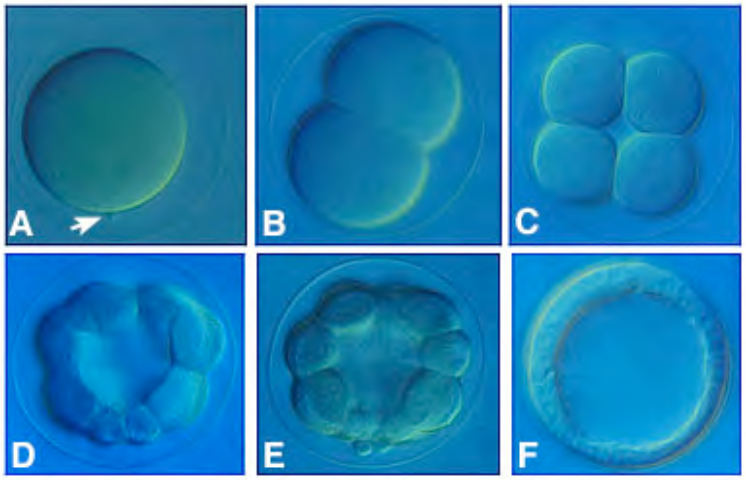
Neutrophils: life as a hun

- ***Neutrophils cruise around looking for unwelcome invaders which they hunt a kill.***
- ***When starved, amoeba can undertake program to form a collective in which s of the cells are sacrificed.***
- ***The bottom line: signaling, detection a decision making are central to cellular***

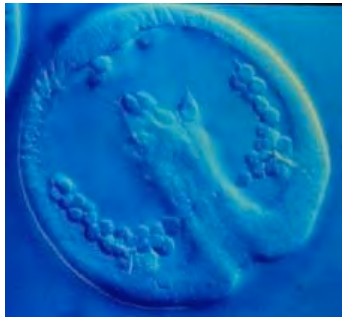
For the greater good: Dictyostelium

How Cells Decide What to Become

Becoming a Sea Urchin

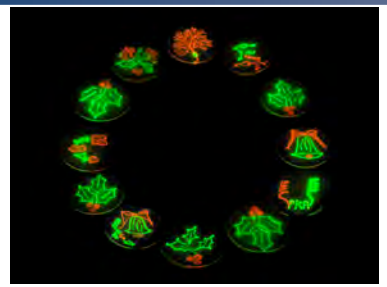


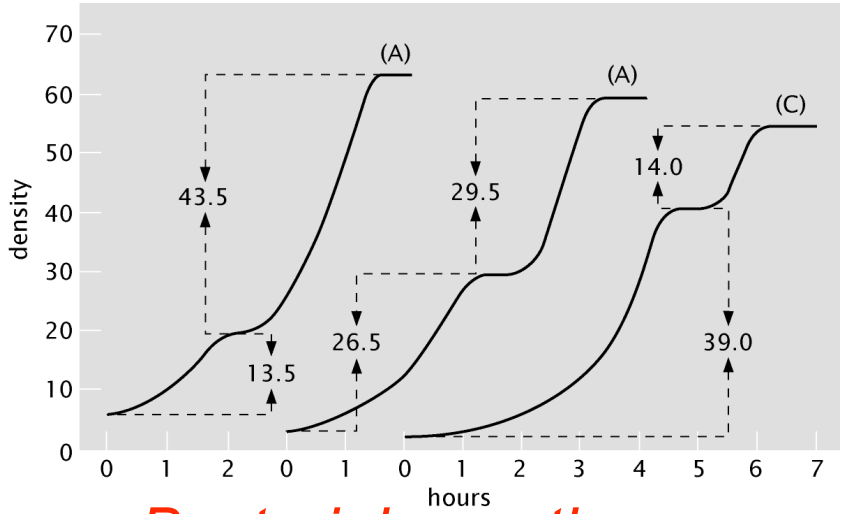
- ***After fertilization, sea urchin embryo undergoes a series of synchronized decisions and differentiation.***
- ***Exquisite control in both space and time.***
- ***The list of examples is virtually endless.***



Forming the Gut

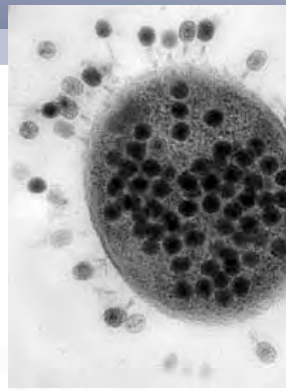
The Development of the Operon Concept: What Cells Eat and When They Die

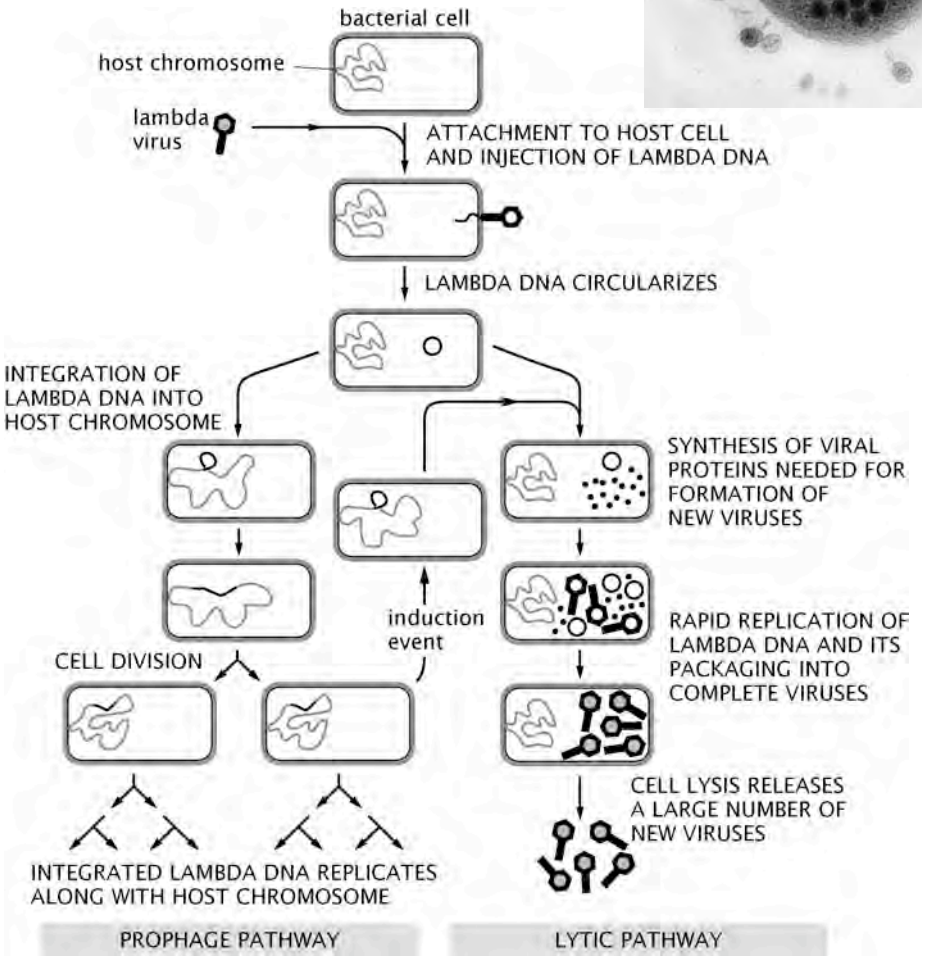




Bacterial growth curves

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

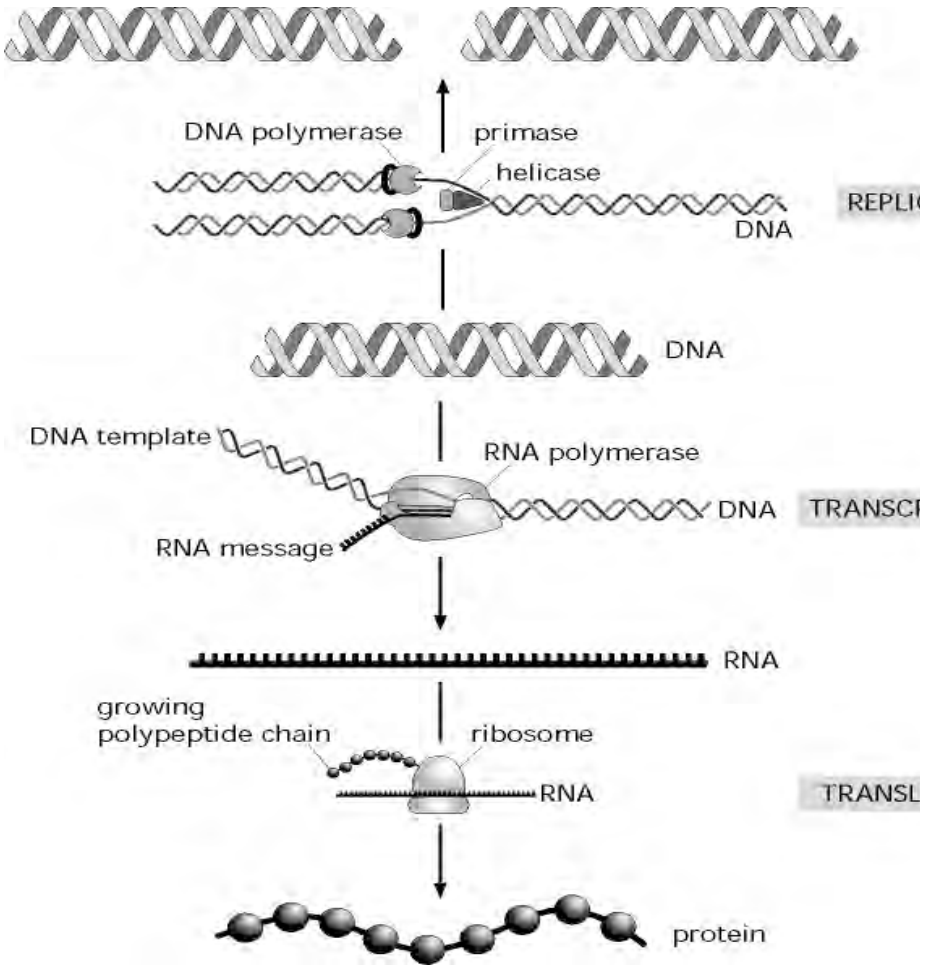




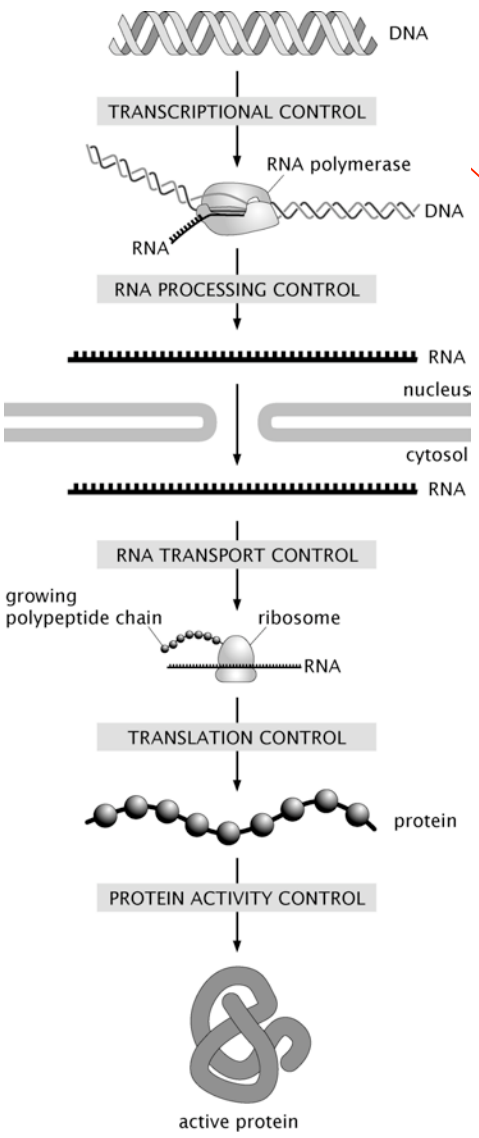
Gene Expression and the Central Dogma

Managing the Great Polymer Langu

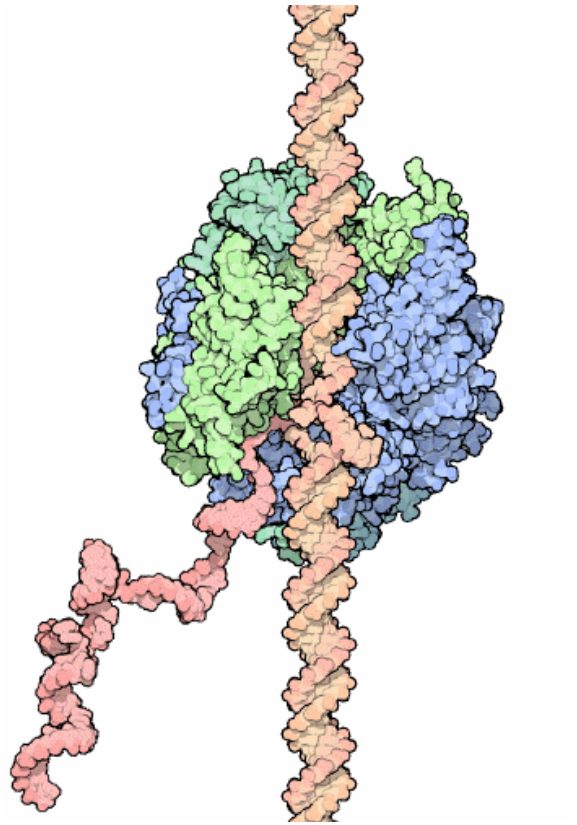
- ***The central dogma tells us about the connection between what Crick dubbed "the two great polymer languages".***
- ***Gene expression refers to the chain of processes that relate the informational content of DNA to the protein consequences of that DNA.***



But, Genes Are Precisely Controlled: Transcriptional Regulation



- ***Regulation takes place very far upstrea***
  In particular, the "decision" is made whether or not to produce mRNA.
- ***Question: What are the molecules that mediate this control?***



Repressors: The Cartoon

- ***Repressor molecules inhibit action of RNA polymerase.***
- ***Repressors can be under the control of other molecules (i.e. inducers) that dictate when repressor is bound and not.***

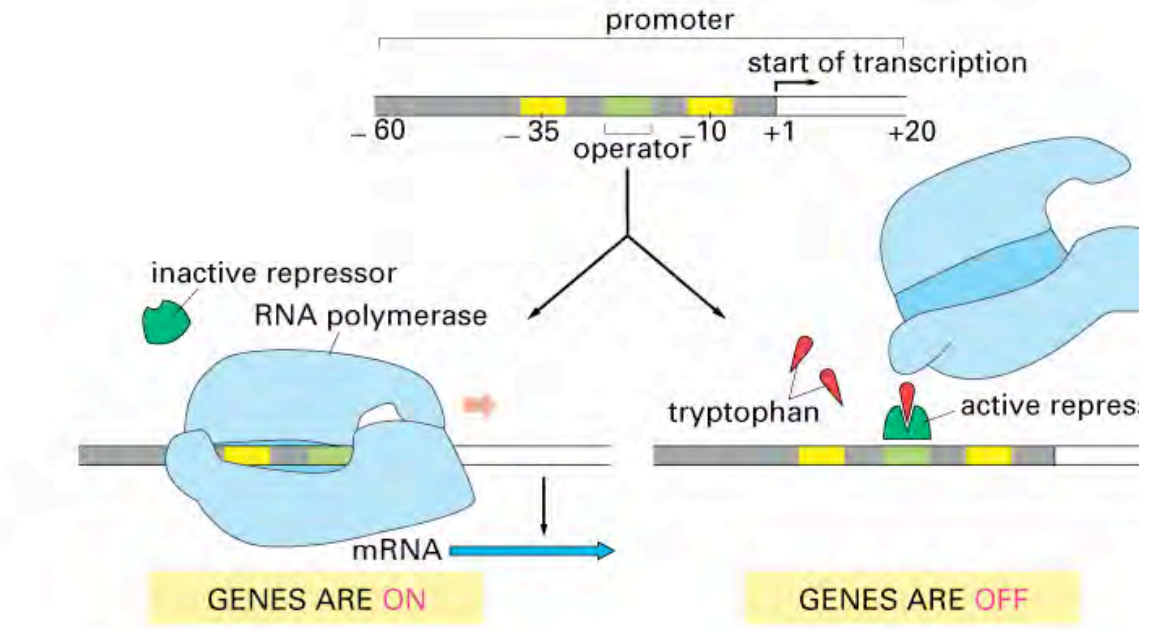
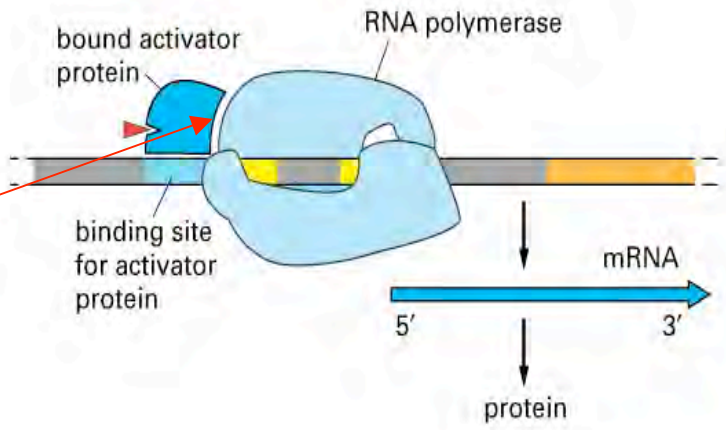


Figure 8-7 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Activators: The Cartoon

- ***Activator molecules enhance the action of RNA polymerase.***
- ***Activators can be under the control of other molecules (i.e. inducers) that dictate when activator is bound and not.***
- ***Activators "RECRUIT" the polymerase.***



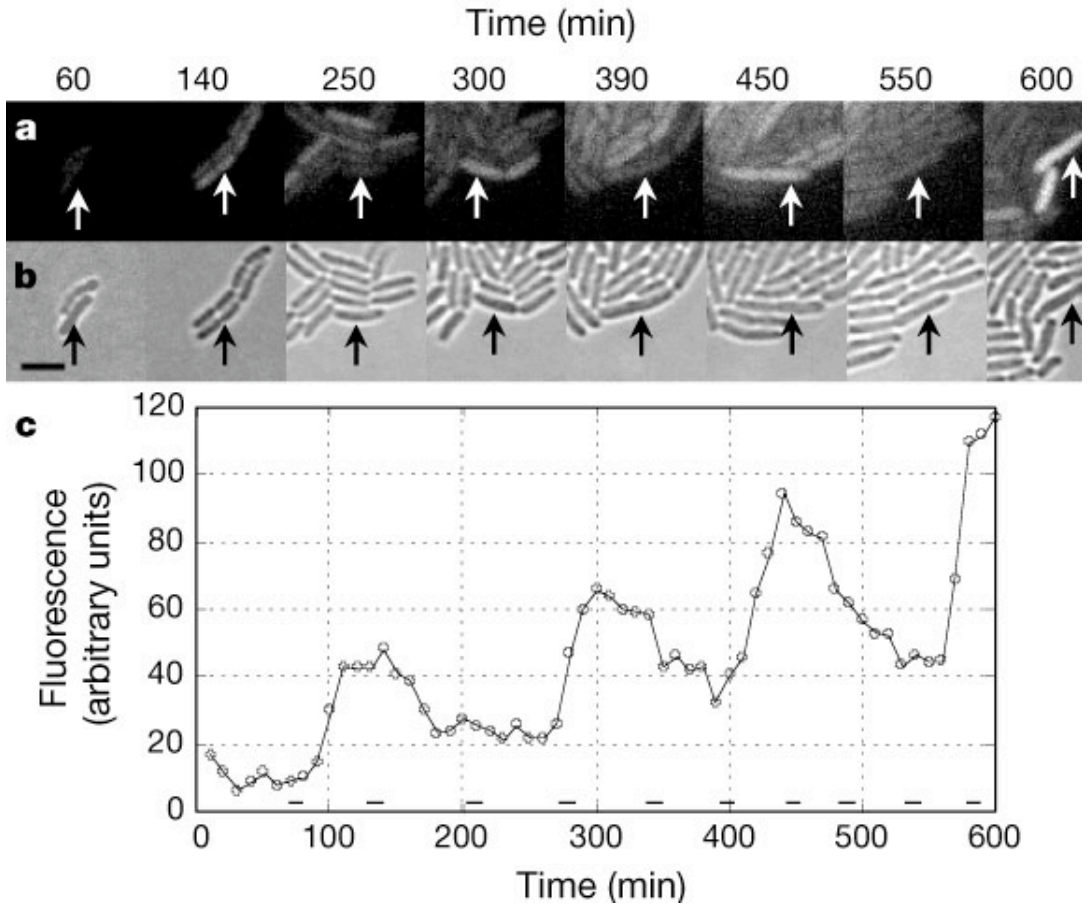
Adhesive interaction between RNAP and activator

But quantitative data demands more than cartoons!

Quantitative Measurement of Gene Expression: When?

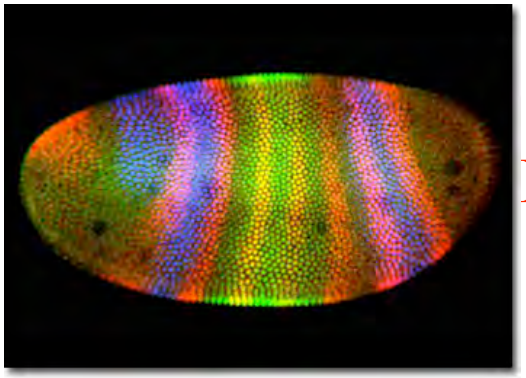
(Elowitz and Leibler)

- *Measurement of when genes are expressed.*
- *An example: the repressilator, a transcriptional regulatory network which leads to a time varying concentration of various gene products.*
- *The idea: stick an engineered set of genes into the cell and then turn them on.*

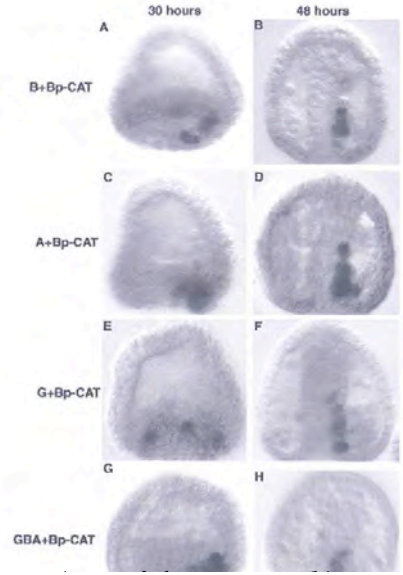


Quantitative Measurement of Gene Expression: Where?

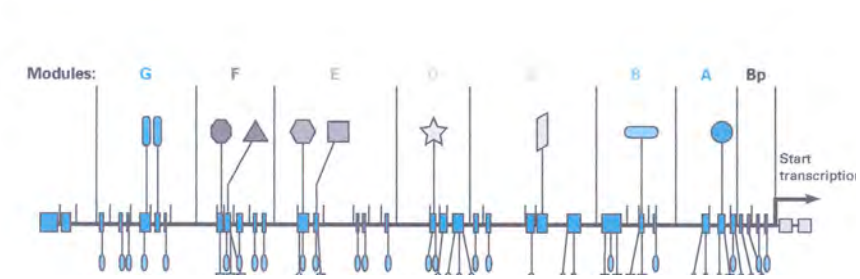
- ***Developmental biology is one of the most compelling arenas for thinking about spacetime gene expression.***

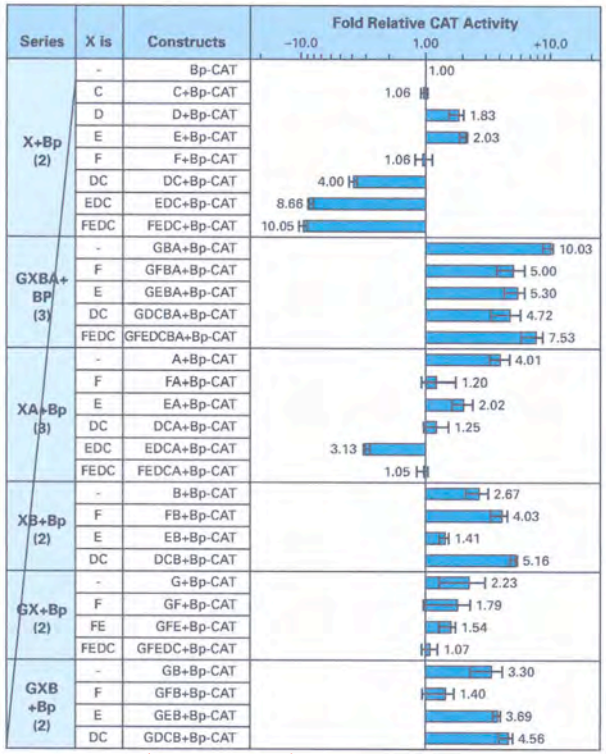


Fruit fly embryo



Sea urchin embryo





Battle cry: quantitative measurements demand quantitative models

The Lac Operon: The Hydrogen Atom of Gene Regulation

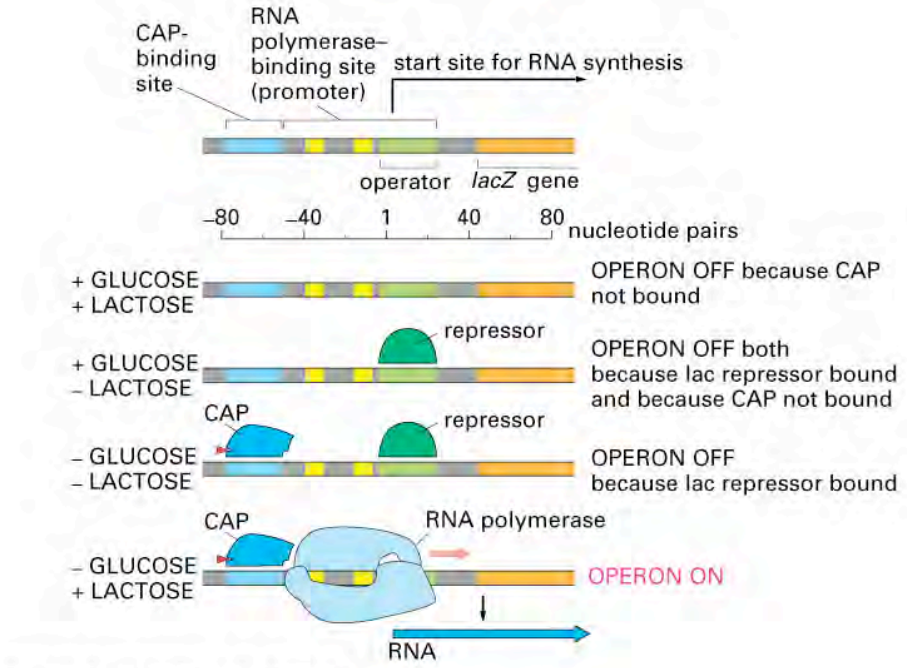


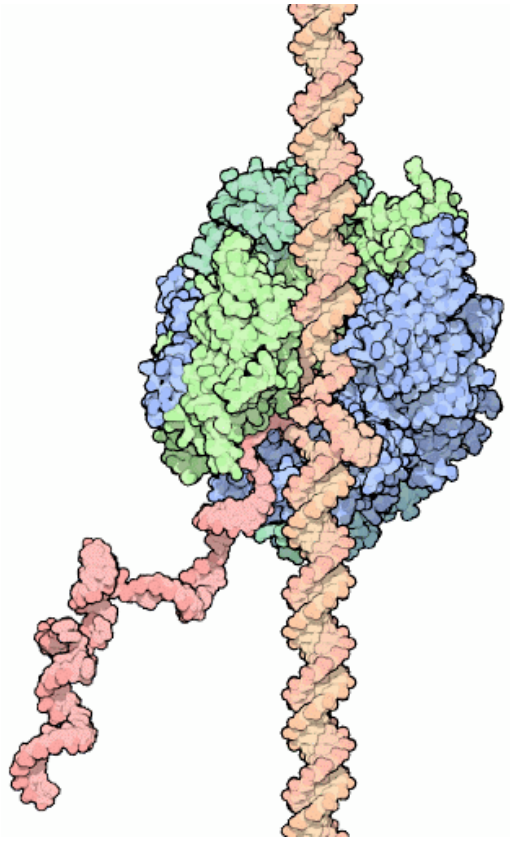
Figure 8-9 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Monod

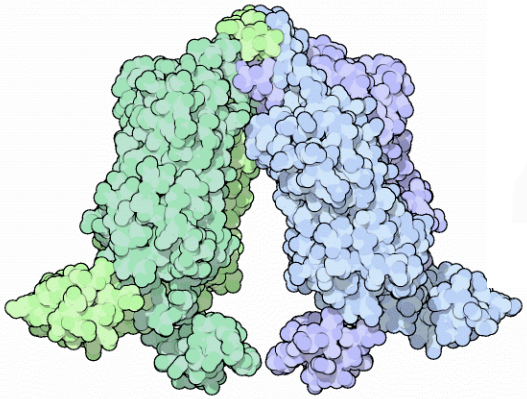
"Tout ce qui est vrai pour le Colibacille est vrai pour l'élép

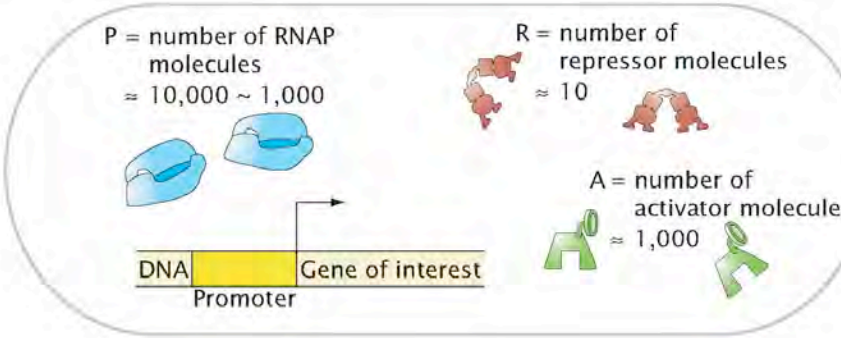
The Single Molecule Census

RNAP+DNA+mRNA

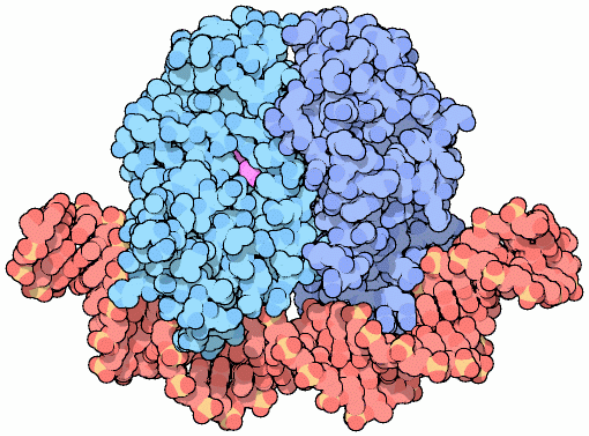


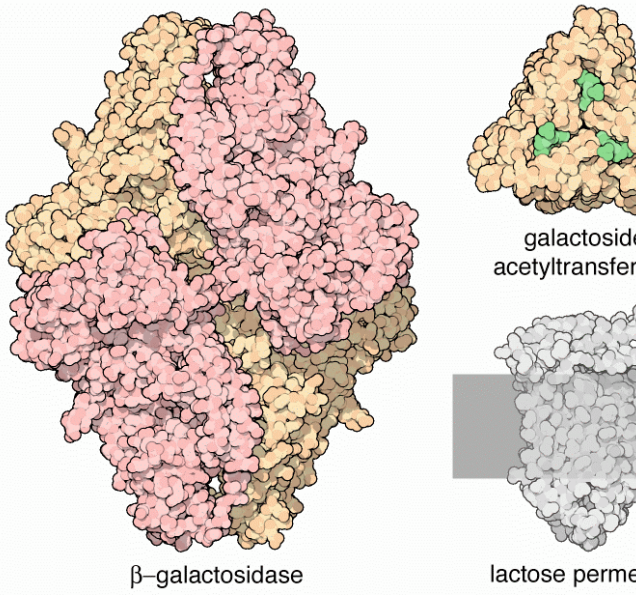
Lac Repressor





CRP and DNA



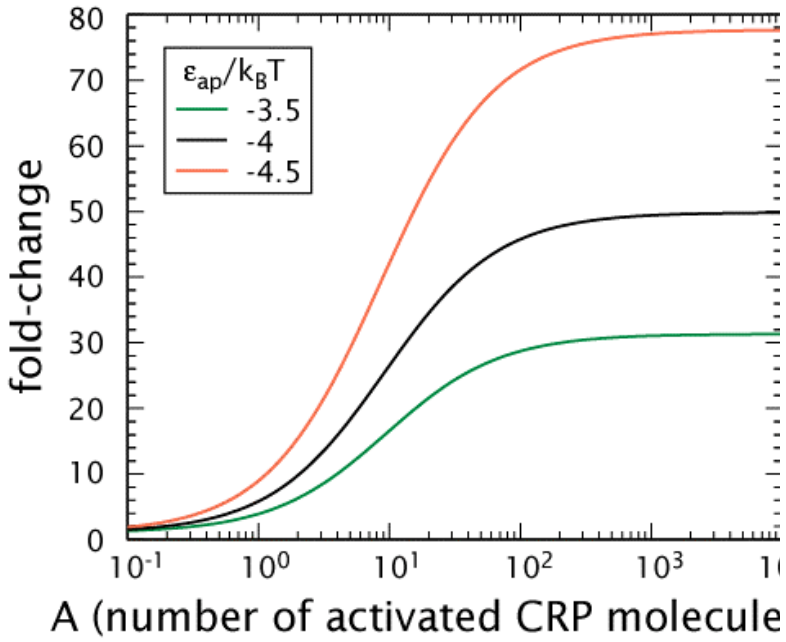


(Beautiful work of David Goodsell

The Notion of Fold-Change

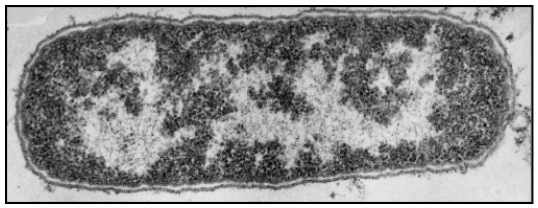
- ***The idea: by how many fold is the expression increased or decreased relative to some reference value.***
- ***To measure fold-change one can measure the expression level (for example using fluorescent reporter molecules) for the case of interest and for the reference state.***

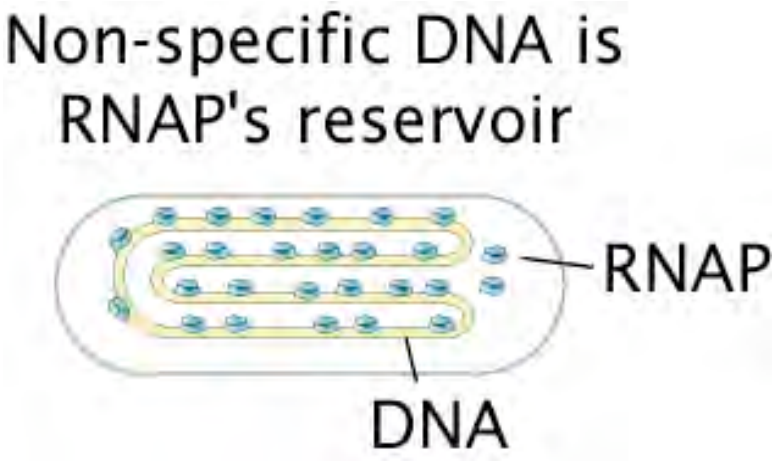
$$\text{fold-change in promoter occupancy} = \frac{p_{bound}(A\neq}{p_{bound}(A=}$$



Statistical Mechanics of Promoter Occupancy

- *The goal: compute the probability of promoter occupancy as a ratio of promoter occupied states to all of the states available to all of the polymerase molecules.*
- *Number of ways of arranging the polymerase molecules is a classic problem in statistics.*

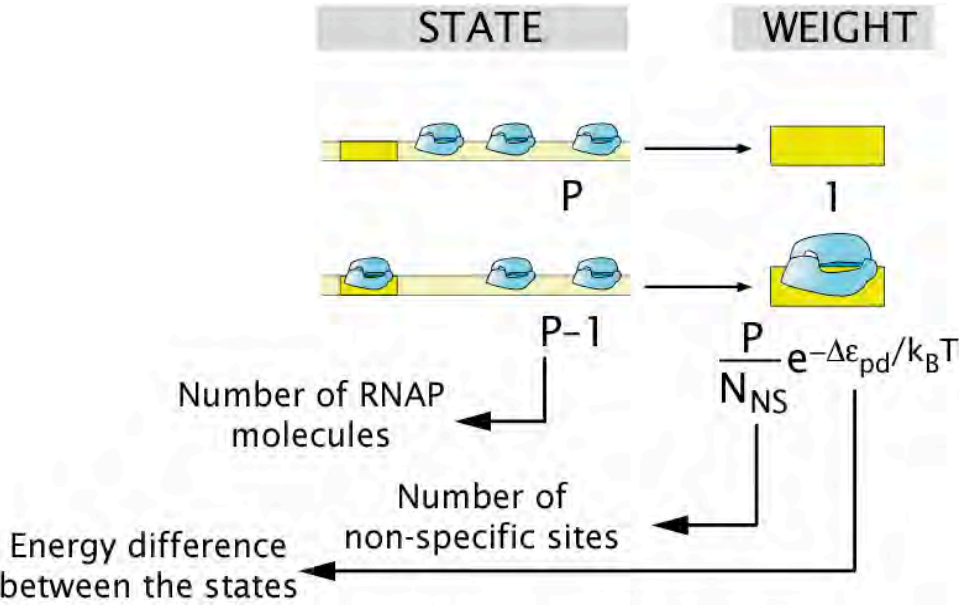




$$Z_{unbound} = \frac{N_{NS}!}{P!(N_{NS}-P)!} e^{-\beta P \epsilon_{pd}^{NS}}$$

Reckoning Promoter Occupancy

- ***We construct the ratio of weights for bound and unbound states.***



$$p_{bound} = \frac{Z_{bound}}{Z_{bound} + Z_{unbour}}$$

$$Z_{unbound} = \frac{N_{NS}!}{P!(N_{NS}-P)!} e^{-\beta P}$$

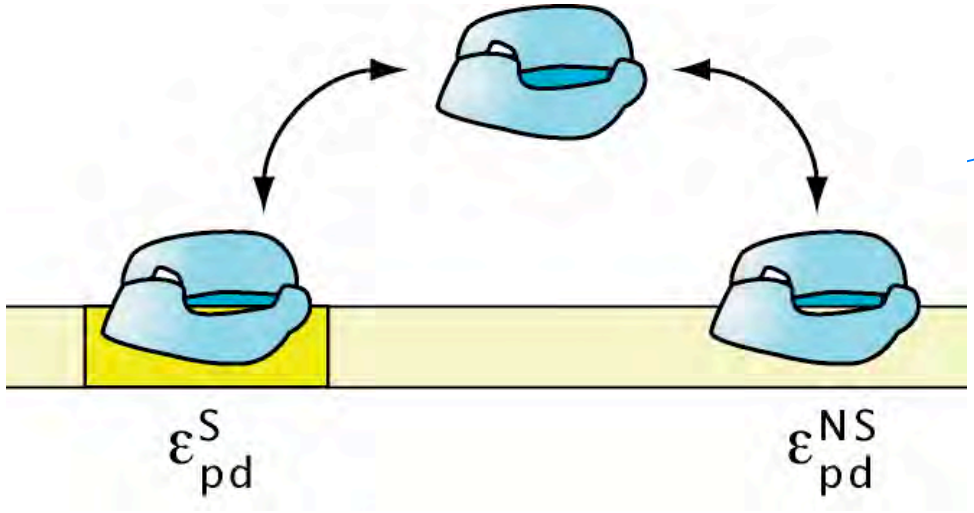
The Outcome:

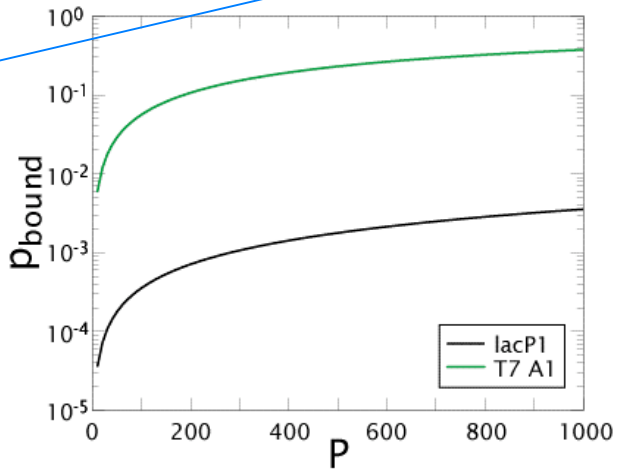
$$p_{bound} = \frac{1}{1 + \frac{N_{NS}}{P} e^{\beta \Delta \epsilon}}$$

Statistical Mechanics of Polymerase Binding: Basal Transcription

10^6

$$p_{bound} = \frac{1}{1+\frac{N_{NS}}{P}e^{\beta\Delta}}$$



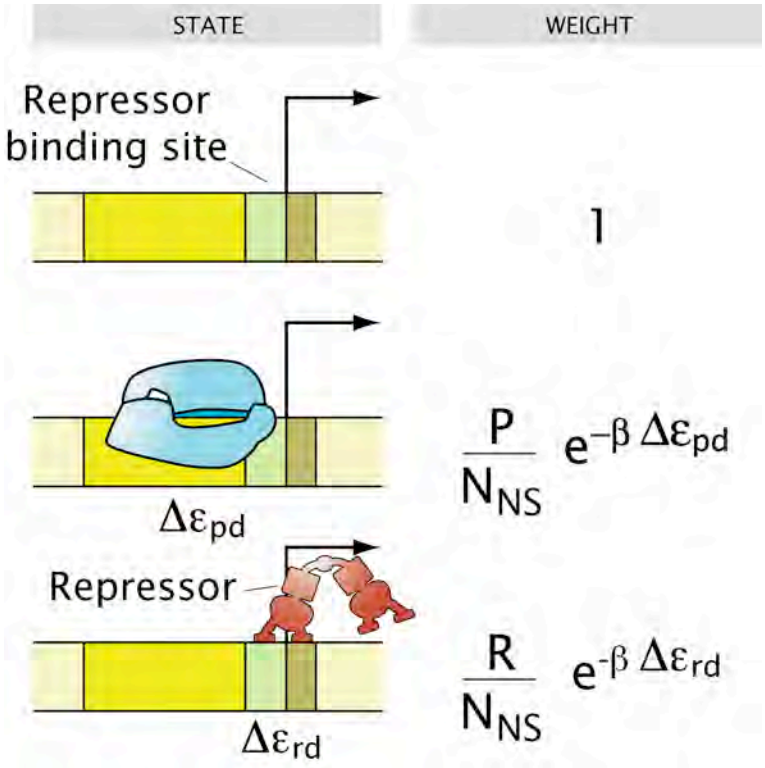


- ***Key insight: RNAP NOT bound in absence of helper molecules for ``normal'' promoters.***
- ***F_{reg} accounts for the presence of regulatory proteins and features such as looping.***

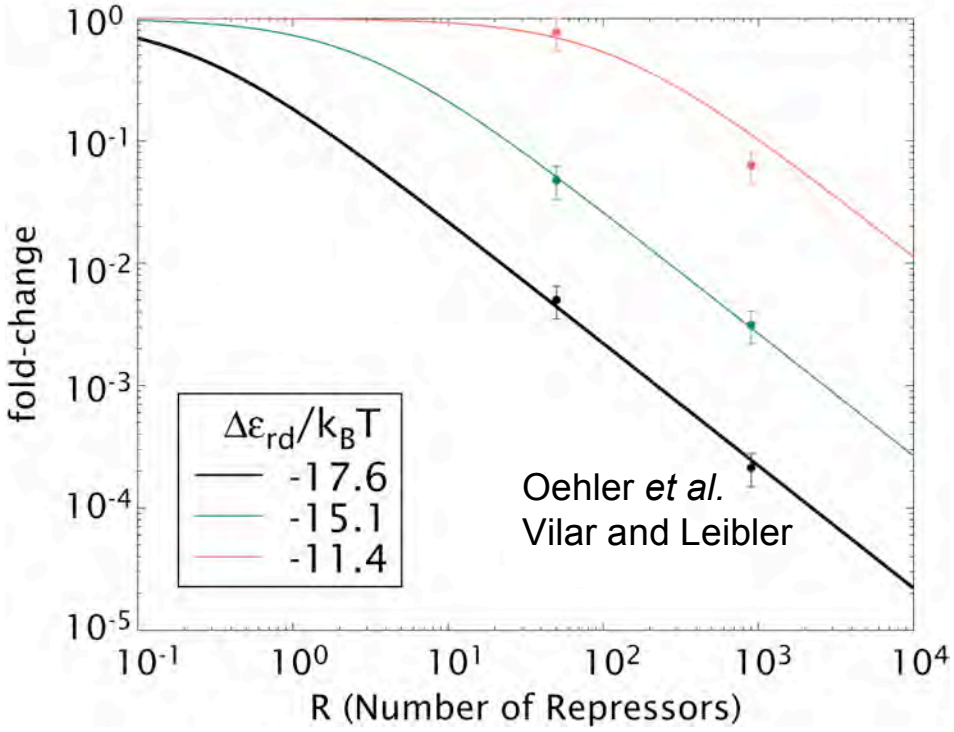
Action of transcription factors the regulation factor

$$p_{bound} = \frac{1}{1+\frac{N_{NS}}{PF_{reg}}e^{\beta\Delta\epsilon}}$$

Statistical Mechanics of a Single Repressor Binding Site



$$F_{reg} = (1 + \frac{R}{N_{NS}} e^{-\beta \Delta \epsilon_{rd}})$$



- ***Model predicts concentration dependence of repression for a single repressor binding site.***
- ***Extent of repression depends upon the strength of the binding site.***

Exploring Regulatory Diversity

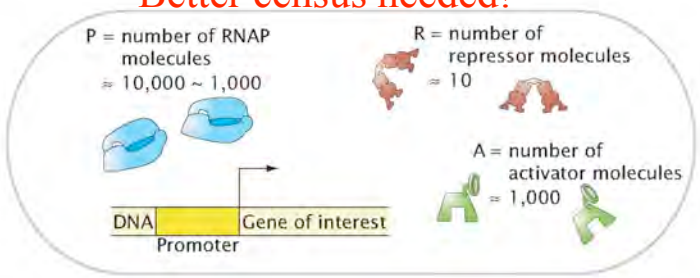
Table 1

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!



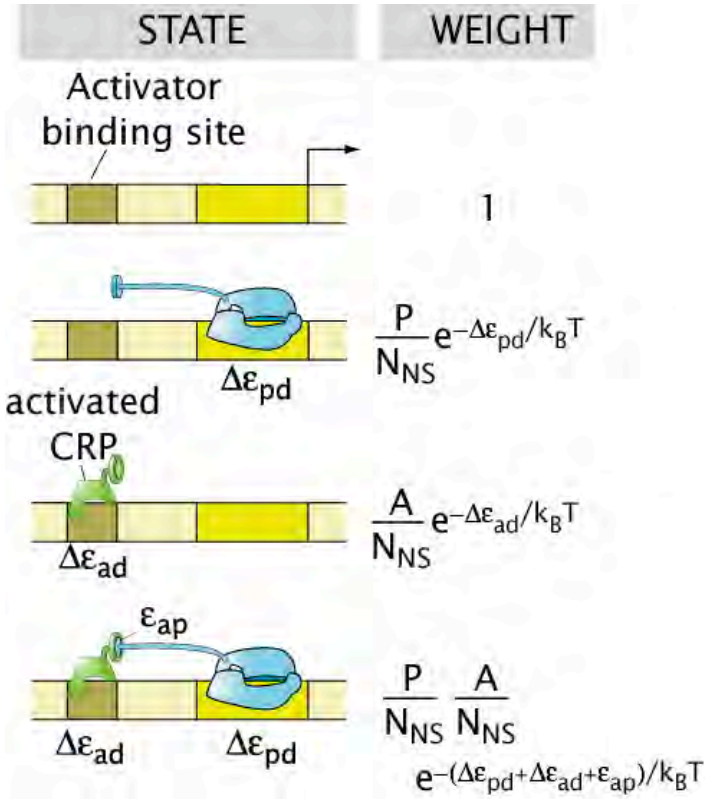
Key point: We can work ou… the regulation factor for ma… other scenarios including other looping scenarios.

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

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

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

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

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

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

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

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

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

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

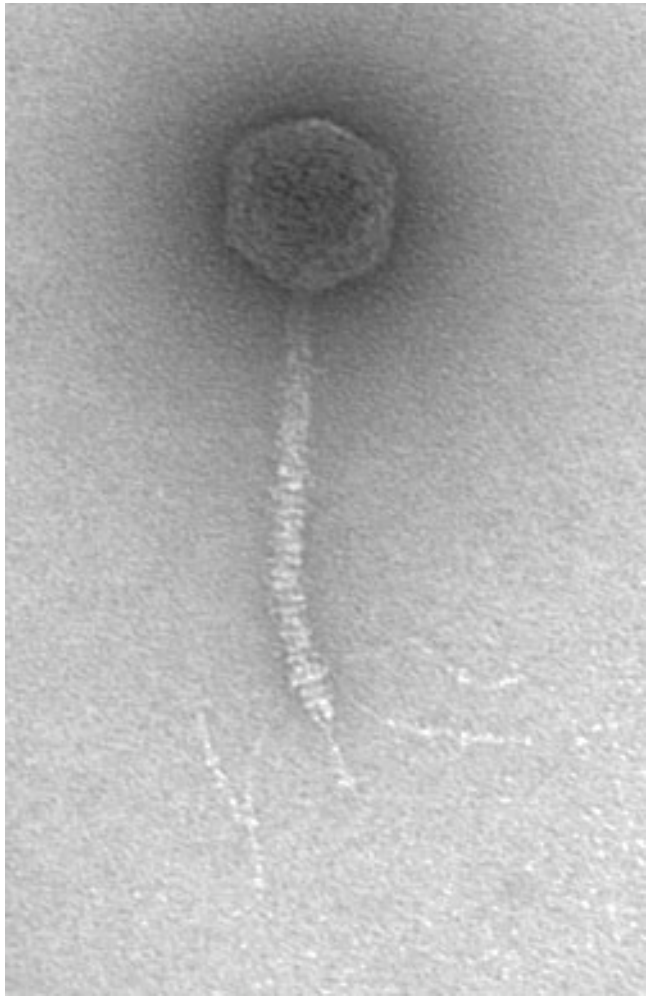
$$\frac{d[Lac_{ext}]}{dt} = -V_{t,Lac}\cdot X$$

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

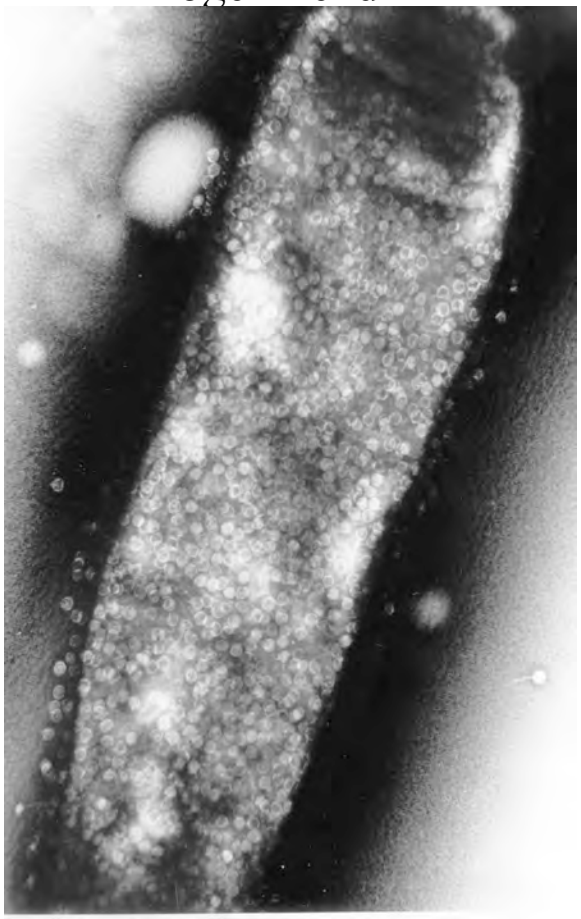
$$\frac{d[Glu6P]}{dt} = V_{t,Glu} + 2\cdot(V_{cat,Lac} + V_{cat,Allo}) - \frac{\mu}{Y_{X/Glu6P}} - \mu\cdot[Glu6P]$$

Wong, Gladney, and Keasling

The Lambda Switch: The Other Hydrogen Atom of Gene Regulation

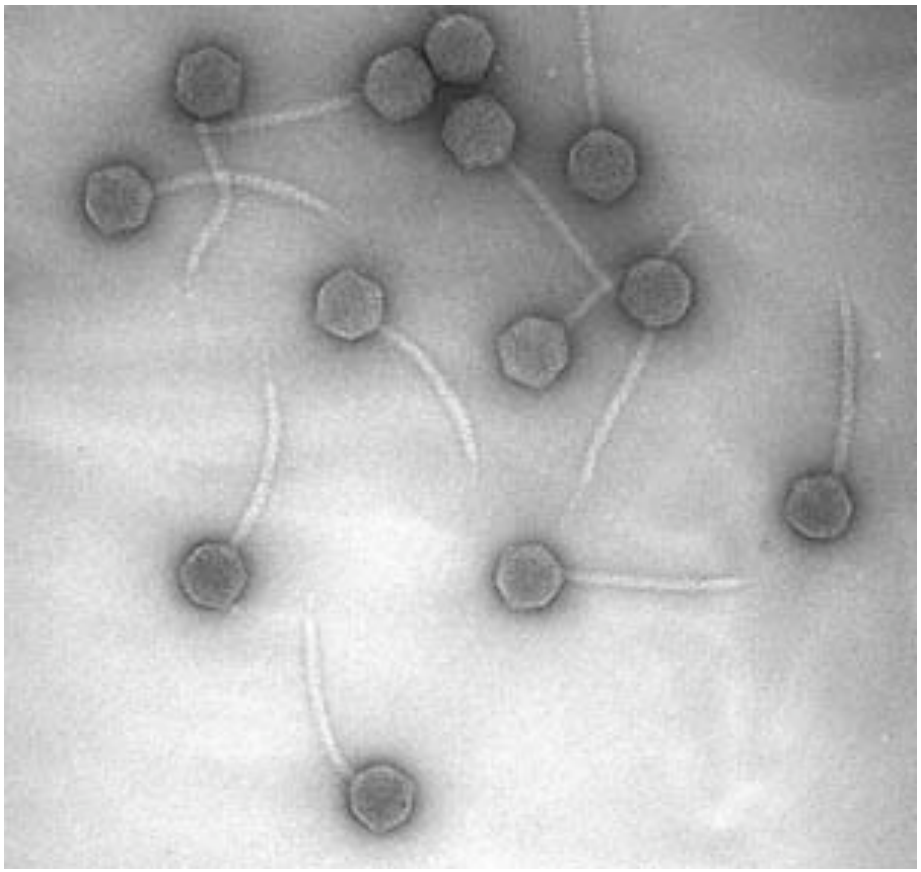


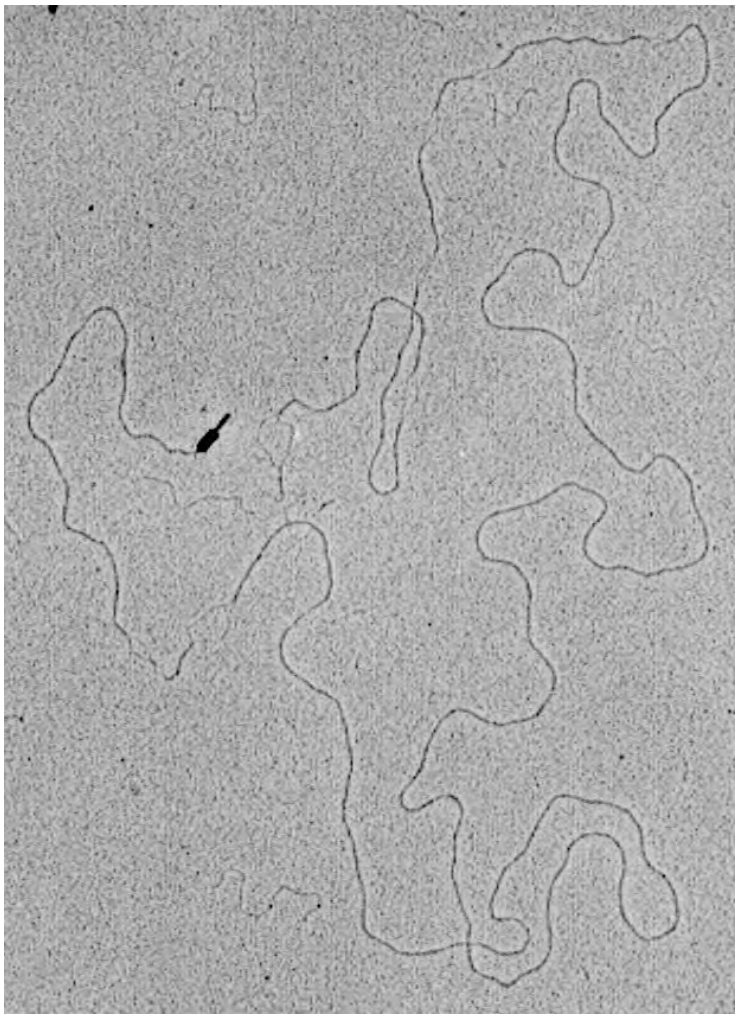
Roger Hendrix



Bacteriophage and Their Genomes

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





The Life Cycle of Bacteriophage Lambda