Lecture 5:
Entropy Rules!

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DEFINITION OF A MICROSTATE

Example: Binding of RNA polymerase to a DNA target site: a simple ligand-receptor binding.

- ***a lattice model*** **of the solution**
- **Ω … number of lattice sites**
- **L … number of ligands**
- **a single receptor**

What is a microstate? [see Fig.]

How many possible microstates is there?

(1) receptor is unoccupied:

$$\Omega!/[L!\,(\Omega - L)!]$$

(2) receptor occupied: $L \rightarrow L - 1$

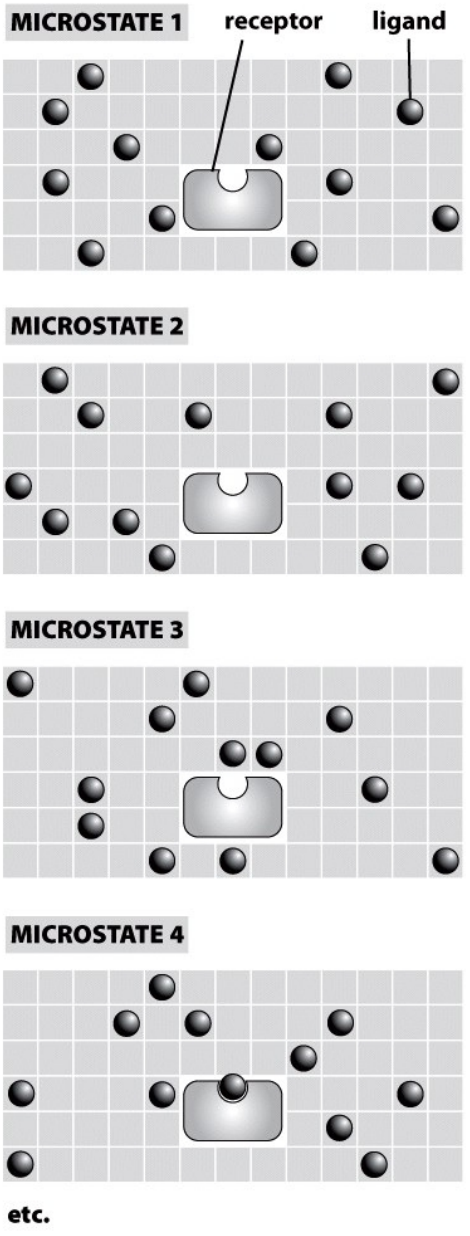


Figure 6.1 Physical Biology of the Cell (© Garland Science 2009)

Another example of microstates: DNA in solution

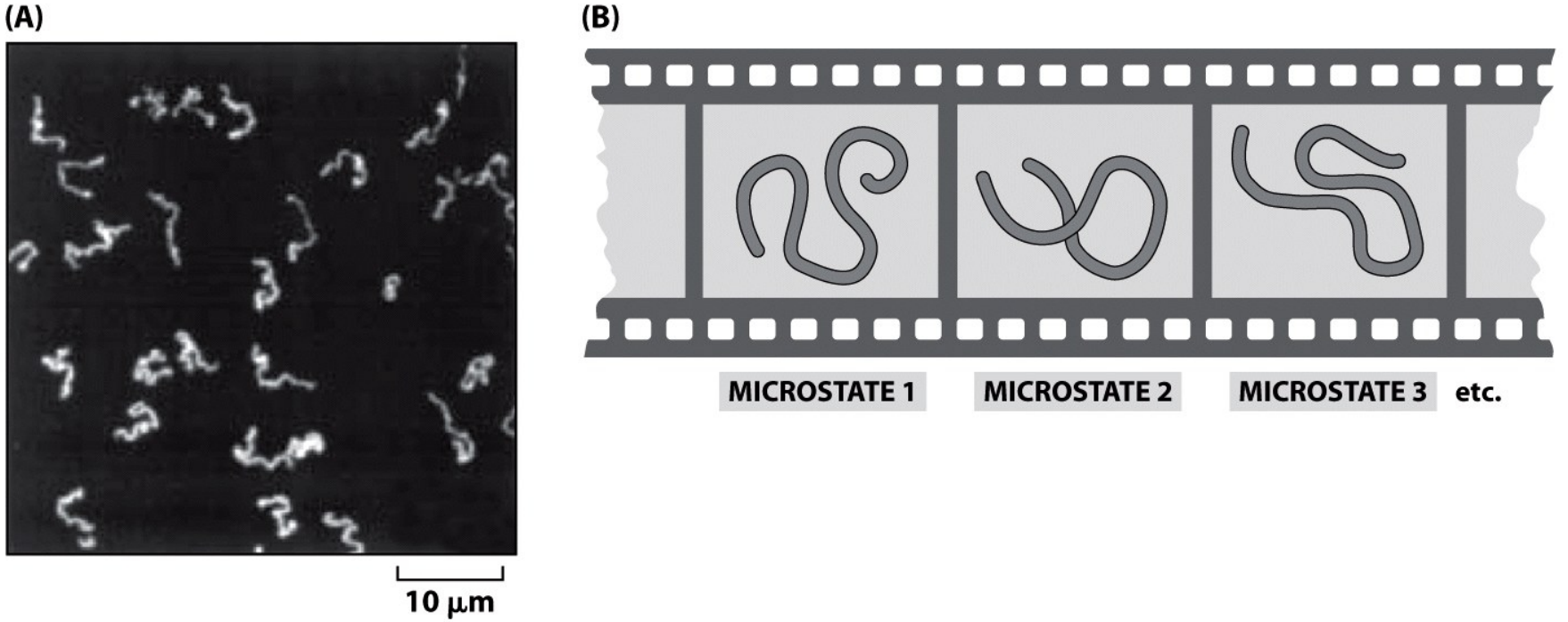


Figure 6.2 Physical Biology of the Cell (© Garland Science 2009)

(A) fluorescence microscopy image of DNA
(B) individual microstates of a single DNA molecule

What is the occurrence probability of each microstate?
Example: A *two-state system* (ion channel: open versus closed)

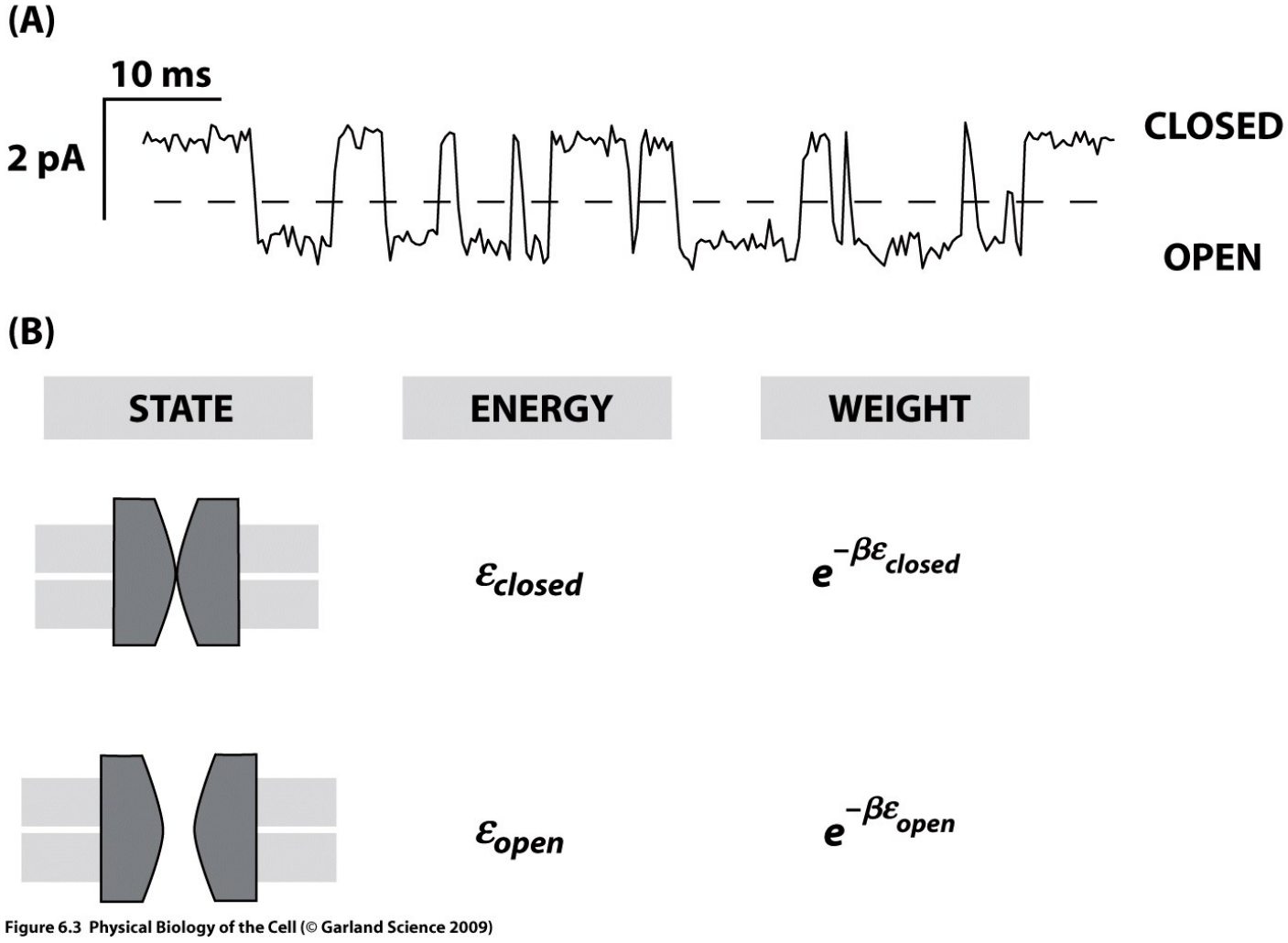


Figure 6.3 Physical Biology of the Cell (© Garland Science 2009)

Two state system: only two microstates exist

- **the time the ion channel is open versus the time the ion channel is closed can be used to calculate the occurrence probabilities, p_{open} and p_{closed}**

- **what determines these probabilities?**

  ***energies of individual microstates,* ε_{open} and ε_{closed}**

The probability of finding a microstate with an energy E_i is

$$p(E_i) = \exp(-E_i/k_B T) / Z$$

The role and identity of Z:

- **probabilities need to be normalized: $\sum_i p(E_i) = 1$**
- ***Z* is known as *the partition function***

$Z = \sum_i \exp(-E_i/k_B T)$ … sum over all microstates

Why do we need the probabilities and the partition function?

$\langle E \rangle = \sum_i E_i \, p(E_i) = Z^{-1} \sum_i E_i \exp(-E_i/k_B T)$ … calculate the average quantities (e.g. average energy)

Useful expressions in terms of $\beta = (k_B T)^{-1}$

$$\langle E \rangle = - Z^{-1} \partial Z/\partial\beta = - \partial(\ln Z)/\partial\beta$$

Ligand-Receptor Binding:

binding of oxygen to hemoglobin
binding of transcription factors to DNA

How do we calculate the probability of receptor binding?

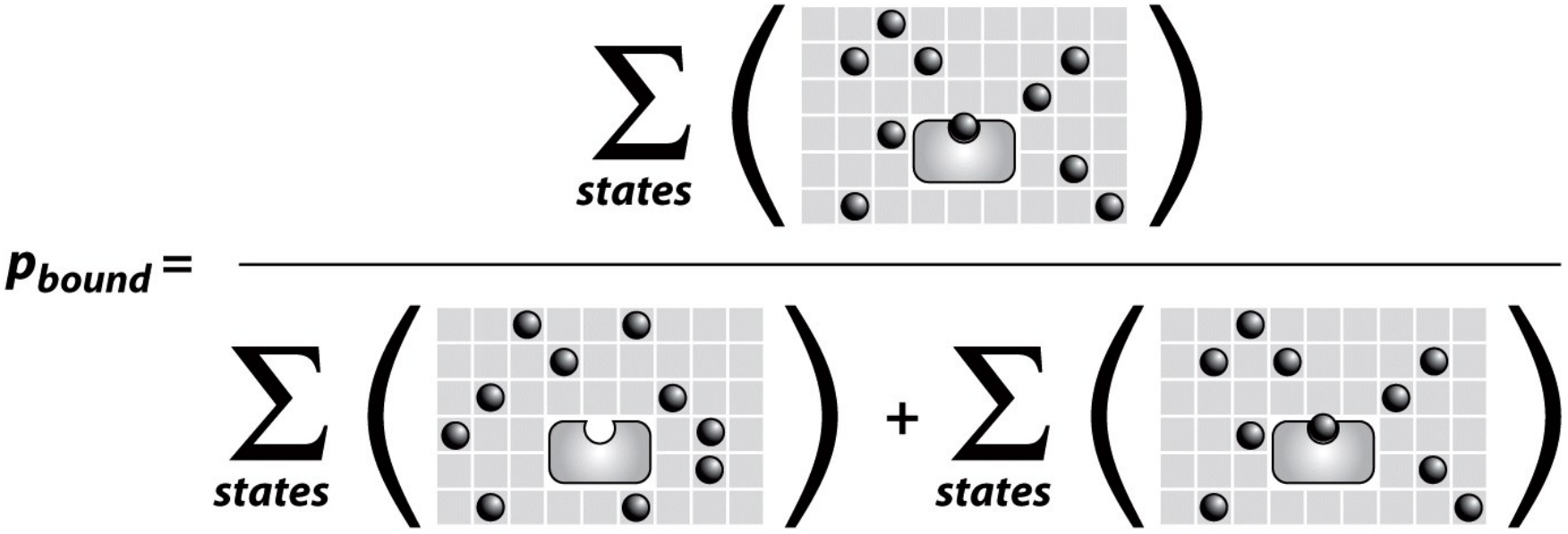


Figure 6.5 Physical Biology of the Cell (© Garland Science 2009)

There are many microstates in which the receptor is bound and many microstates in which no binding takes place:
multiplicities of the two states

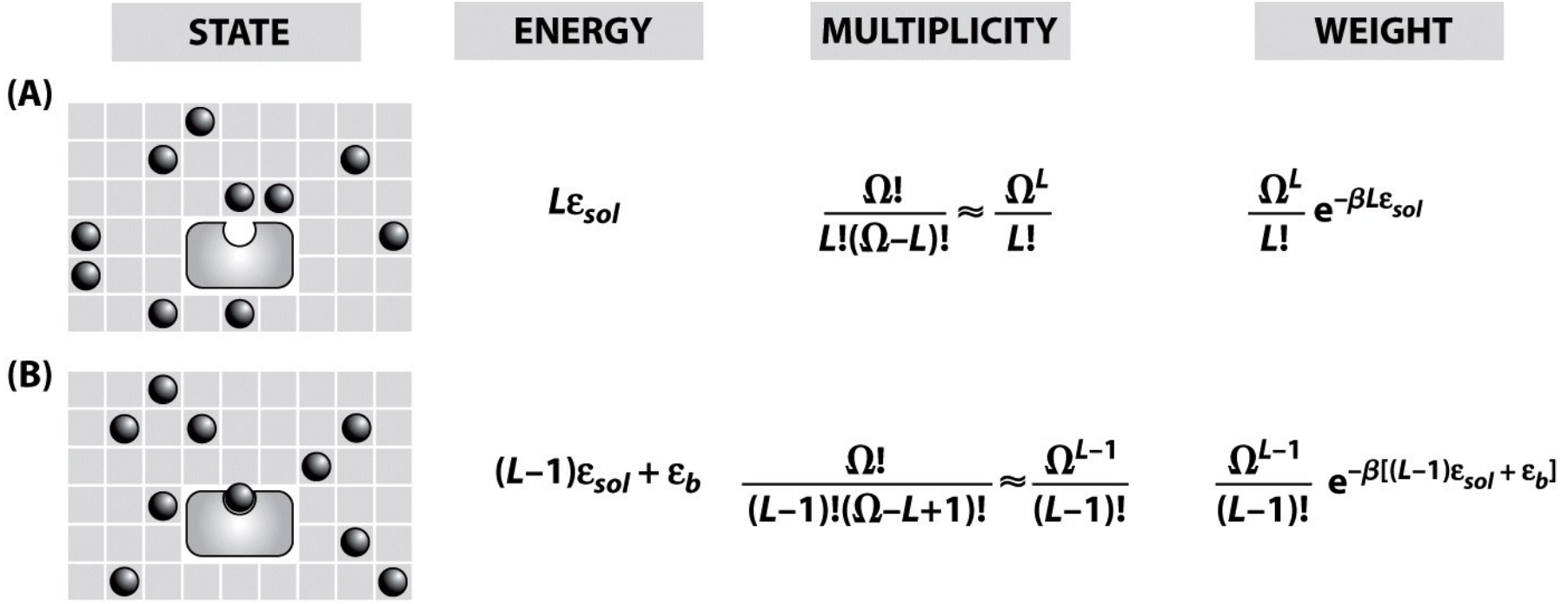


Figure 6.4 Physical Biology of the Cell (© Garland Science 2009)

Weight for a situation in which a receptor is bound:

$$\text{weight (bound)} = \exp(-\beta\varepsilon_b) \times \sum_{sol} \exp[-\beta(L-1)\varepsilon_{sol}]$$

$$\sum_{sol} \exp[-\beta(L-1)\varepsilon_{sol}] = \text{multiplicity} \times \exp[-\beta(L-1)\varepsilon_{sol}]$$

$$= \Omega!/[(L-1)!\,(\Omega-L+1)!]\ \exp[-\beta(L-1)\varepsilon_{sol}]$$

$$\text{weight (bound)} = \Omega!/[(L-1)!\,(\Omega-L+1)!]\ \exp[-\beta\varepsilon_\beta-\beta(L-1)\varepsilon_{sol}]$$

$$\text{weight (unbound)} = \Omega!/[L!\,(\Omega-L)!]\ \exp[-\beta L\varepsilon_{sol}]$$

Partition function:

$$Z(L,\Omega) = \text{weight (bound)} + \text{weight (unbound)}$$

Useful approximation for the case $L \ll \Omega$:

$$\Omega!/(\Omega - L)! = \Omega^L$$

Can be derived using Stirling's approximation: $\ln(N!) = N \ln N - N$

$$\ln[\Omega!/(\Omega - L)!] = \ln\Omega! - \ln(\Omega - L)! \approx \Omega \ln\Omega - \Omega - (\Omega - L)$$
$$\ln(\Omega - L) + (\Omega - L) \approx \Omega \ln\Omega - (\Omega - L)\ln(\Omega - L) =$$
$$\ln[\Omega^{\Omega} (\Omega - L)^L / (\Omega - L)^{(\Omega - L)}] \approx \ln[\Omega^{\Omega} \Omega^L (\Omega - L)^L / \Omega - L)^{\Omega}] \approx$$
$$\ln \Omega^L$$

Thus, we can calculate p_{bound} as:

$$p_{bound} = (L/\Omega) \exp(-\beta\Delta\varepsilon) / [1 + (L/\Omega) \exp(-\beta\Delta\varepsilon)]$$
$$p_{bound} = (c/c_0) \exp(-\beta\Delta\varepsilon) / [1 + (c/c_0) \exp(-\beta\Delta\varepsilon)]$$

Classical result: a competition between energetic and entropic contributions to the free energy: $c/c_0 = ½$ … half occupancy

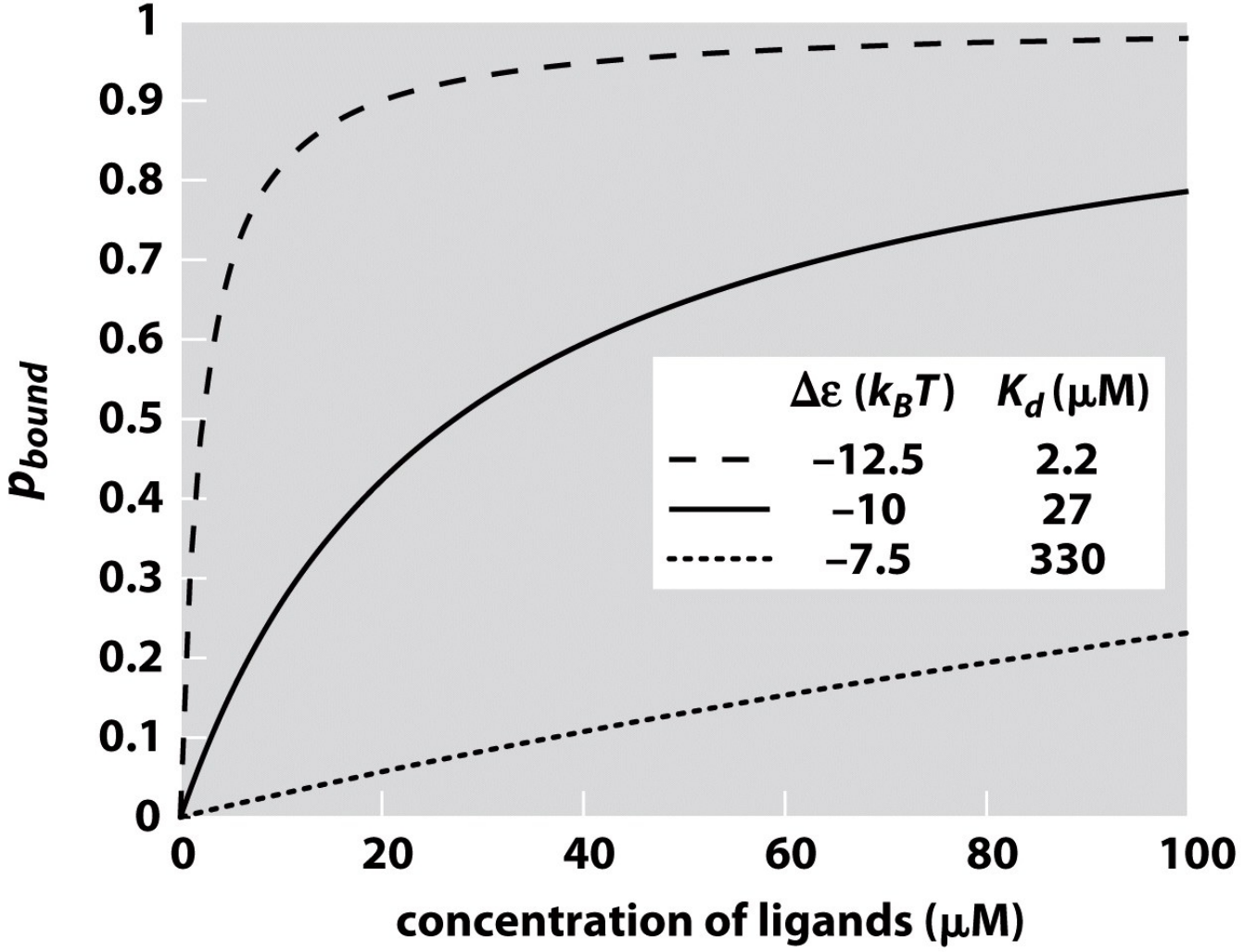


Figure 6.6 Physical Biology of the Cell (© Garland Science 2009)

Statistical Mechanics of Gene Expression: RNA polymerase binding at promotor sites

Cells can control transcription and translation: revised central dogma

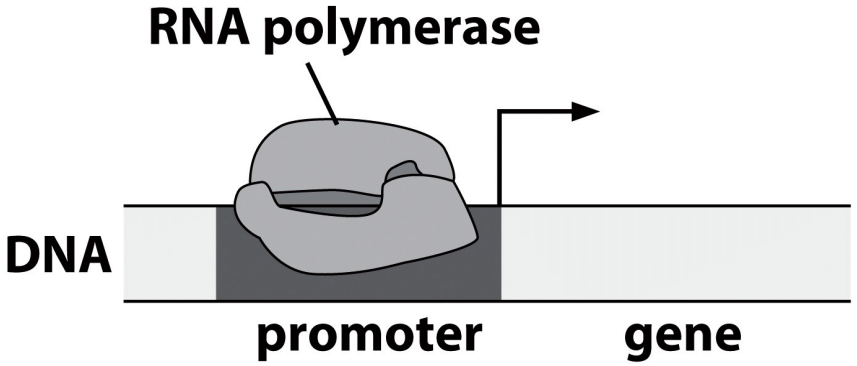


Figure 6.8 Physical Biology of the Cell (© Garland Science 2009)

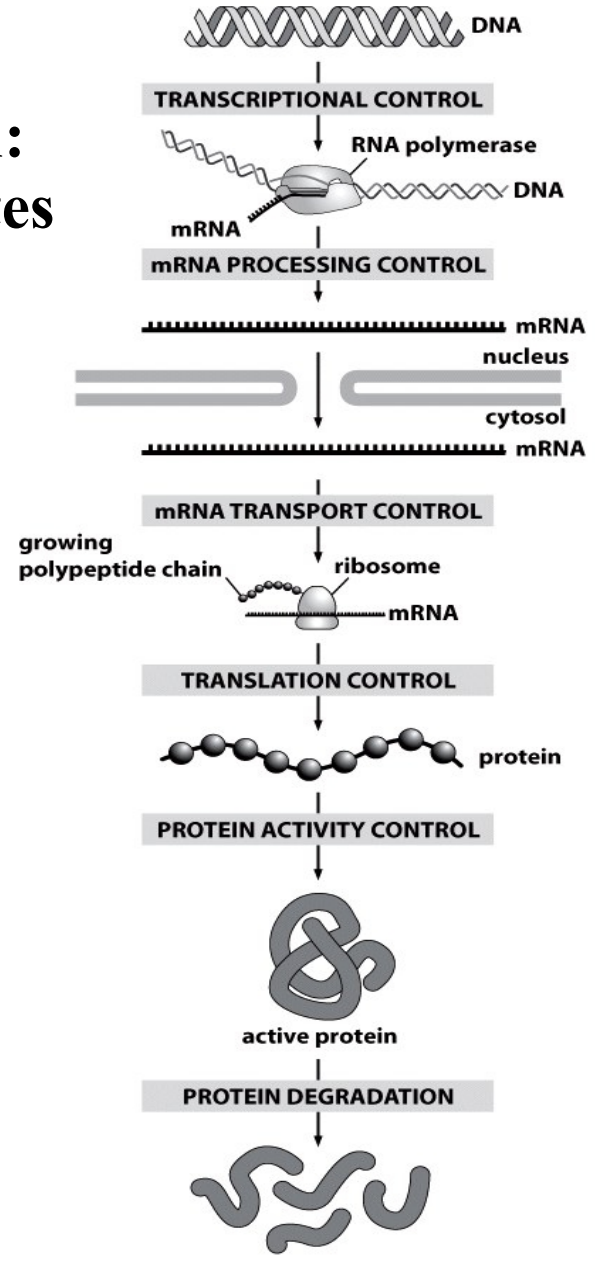


Figure 6.7 Physical Biology of the Cell (© Garland Science 2009)

***Transcription*: a process that begins once the polymerase Escaped the promotor and moves along the gene (part of DNA) And results in creation of mRNA molecule (*a transcript*).**

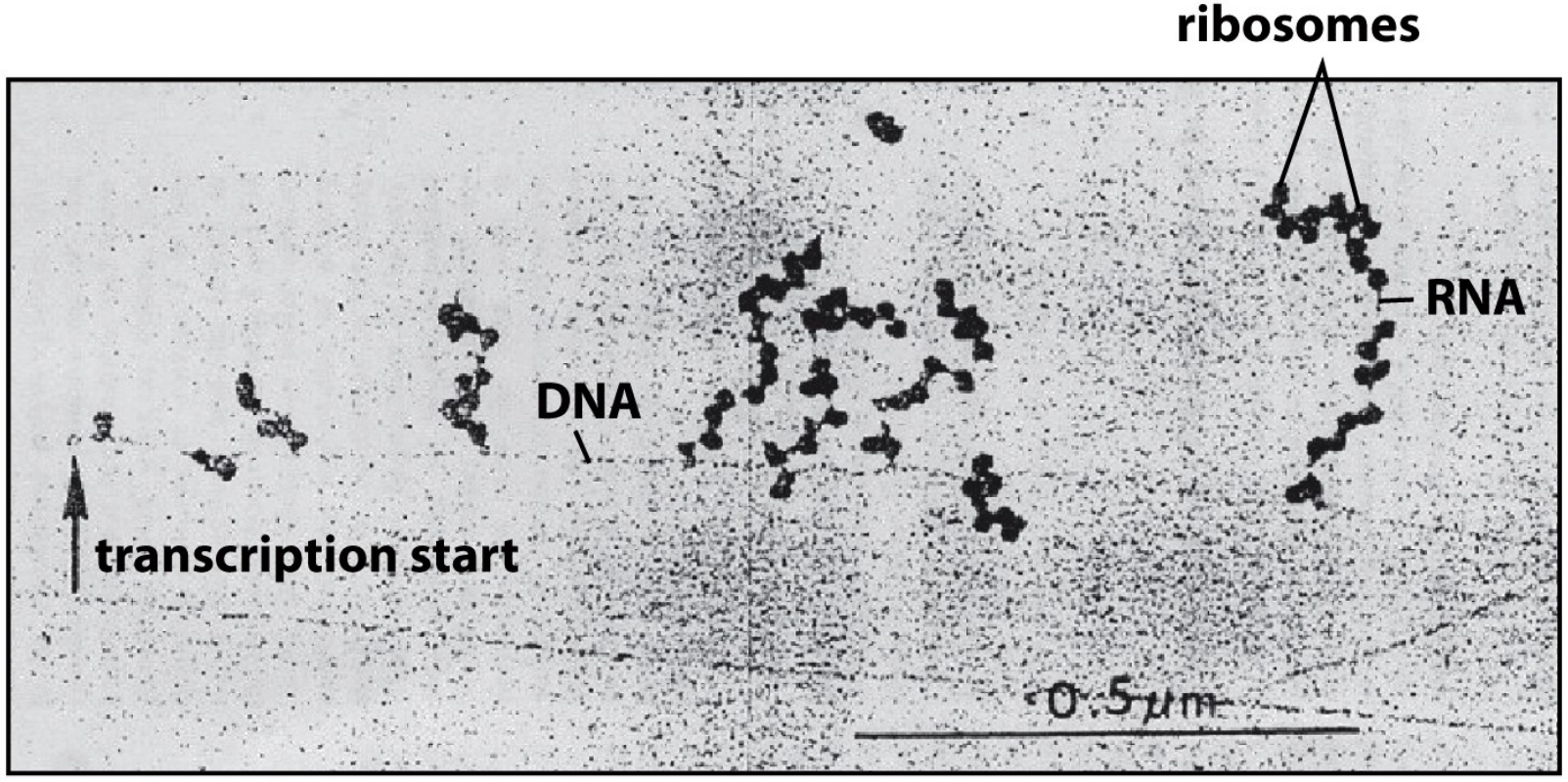


Figure 3.9 Physical Biology of the Cell (© Garland Science 2009)

a microscopy image of transcription

Experimental evidence: thousands of RNA polymerase molecules in *E. coli* bound to the DNA promoter sites

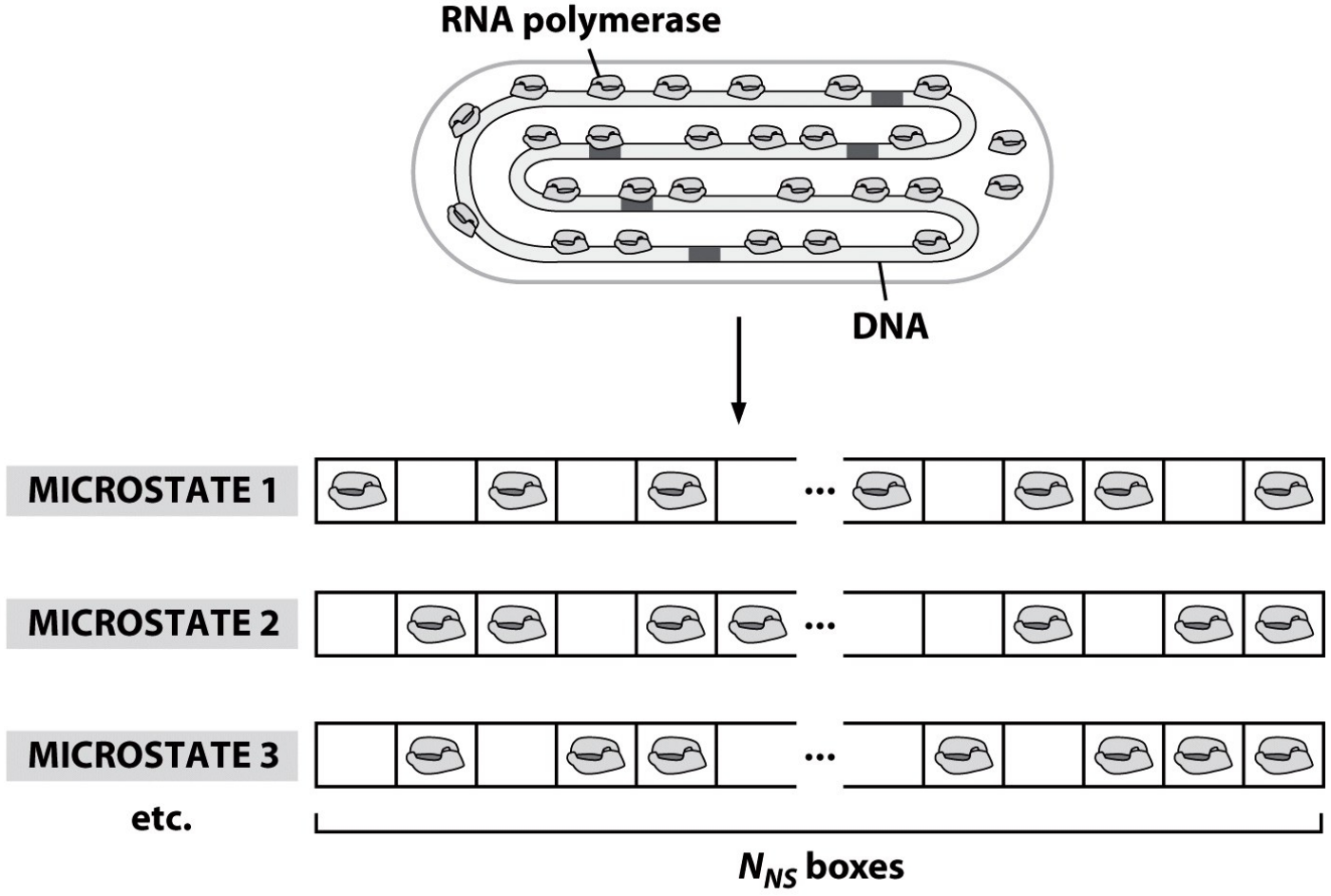


Figure 6.9 Physical Biology of the Cell (© Garland Science 2009)

Simplest model of RNA polymerase binding to DNA:

DNA modeled as:

-N_{NS} distinct boxes (NS … non-specific sites)

-P number of RNA polymerase molecules

(only one molecule per non-specific DNA site)

Partial partition function for non-specific binding:

$$Z_{NS}(P, N_{NS}) = N_{NS}!/[P!\,(N_{NS}-P)!]\,\exp(-\beta P \varepsilon^{NS}_{pd})$$

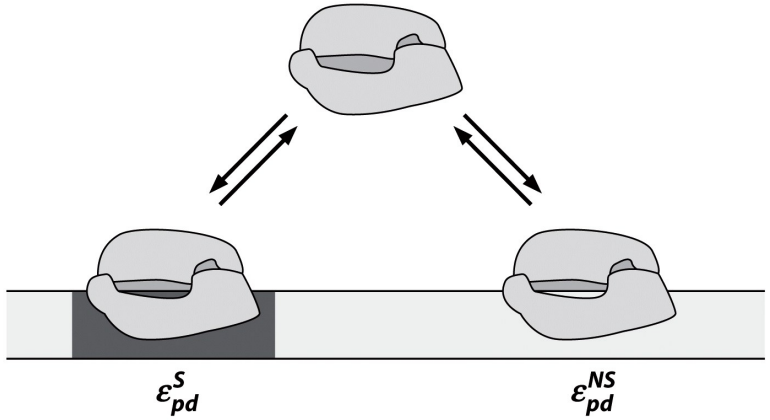


Figure 6.10 Physical Biology of the Cell (© Garland Science 2009)

The total partition function is a sum of two parts:

[no RNAP on promoter] + [one RNAP on promoter]

$$Z(P, N_{NS}) = Z_{NS}(P, N_{NS}) + Z_{NS}(P-1, N_{NS}) \exp(-\beta \varepsilon^{S}_{pd})$$

Probability of one RNAP bound to the promoter site is:

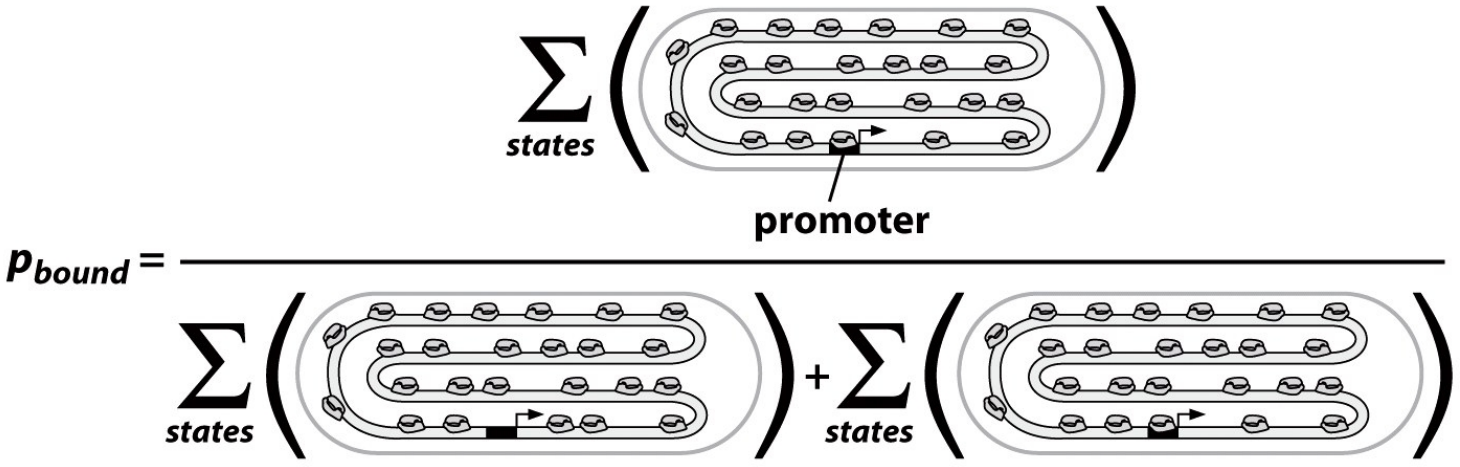


Figure 6.12 Physical Biology of the Cell (© Garland Science 2009)

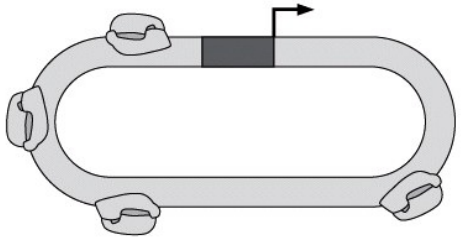
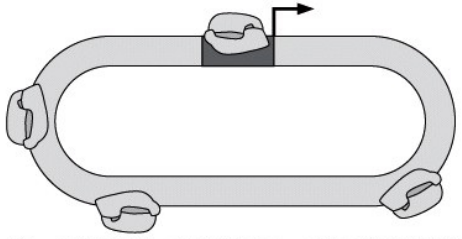
STATE	ENERGY	MULTIPLICITY	WEIGHT (MULTIPLICITY x BOLTZMANN WEIGHT)
	$P\varepsilon_{pd}^{NS}$	$\frac{N_{NS}!}{P!\,(N_{NS}-P)!} \approx \frac{(N_{NS})^P}{P!}$	$\frac{(N_{NS})^P}{P!}\ e^{-P\varepsilon_{pd}^{NS}/k_BT}$
	$(P-1)\varepsilon_{pd}^{NS} + \varepsilon_{pd}^{S}$	$\frac{N_{NS}!}{(P-1)!\,[N_{NS}-(P-1)]!} \approx \frac{(N_{NS})^{P-1}}{(P-1)!}$	$\frac{(N_{NS})^{P-1}}{(P-1)!}\ e^{-(P-1)\varepsilon_{pd}^{NS}/k_BT}\ e^{-\varepsilon_{pd}^{S}/k_BT}$

Figure 6.11 Physical Biology of the Cell (© Garland Science 2009)

$$p_{bound} =$$

$$Z_{NS}(P-1,N_{NS})\exp(-\beta\varepsilon^{S}_{pd}) / [Z_{NS}(P,N_{NS}) + Z_{NS}(P-1,N_{NS})\exp(-\beta\varepsilon^{S}_{pd})]$$

$$=$$

$$[1 + N_{NS}/P \exp(\beta\Delta\varepsilon_{pd})]^{-1}$$

$$\Delta\varepsilon_{pd} = \varepsilon^{S}_{pd} - \varepsilon^{NS}_{pd}$$

The more negative the difference $\Delta\varepsilon_{pd}$, the higher the probability of binding (lac P1: $-2.9\ k_B T$; T7 A1: $-8.1\ k_B T$).

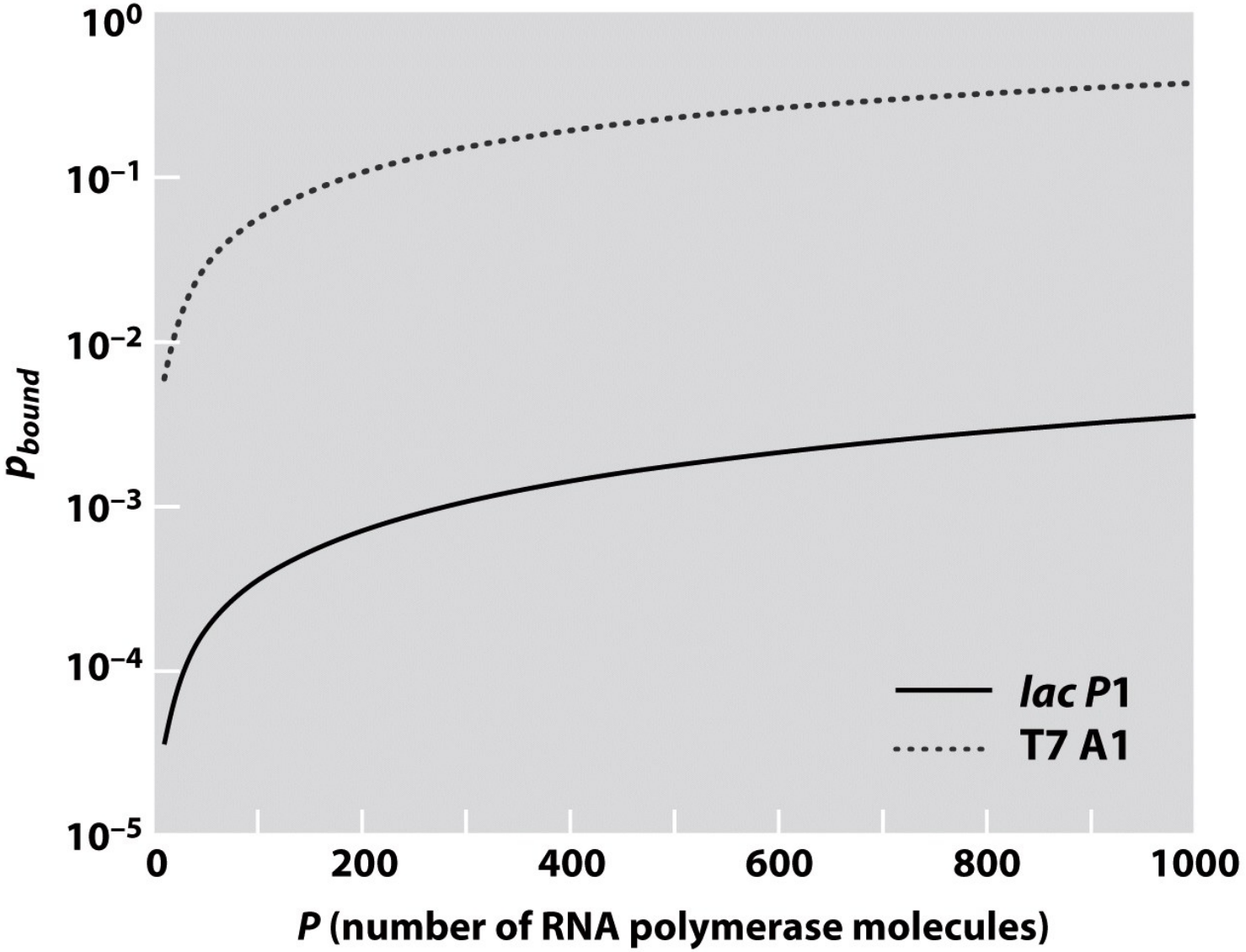


Figure 6.13 Physical Biology of the Cell (© Garland Science 2009)

Classical derivation of the Boltzmann distribution:

system + reservoir = isolated system maximal entropy principle

Fundamental idea:

probability of finding *a microstate of the system* is proportional to *the number of states available to the reservoir* when the system is in its specific microstate:

$$p(E_s^{I})/p(E_s^{II}) = W_r(E_{tot} - E_s^{I})/W_r(E_{tot} - E_s^{II})$$

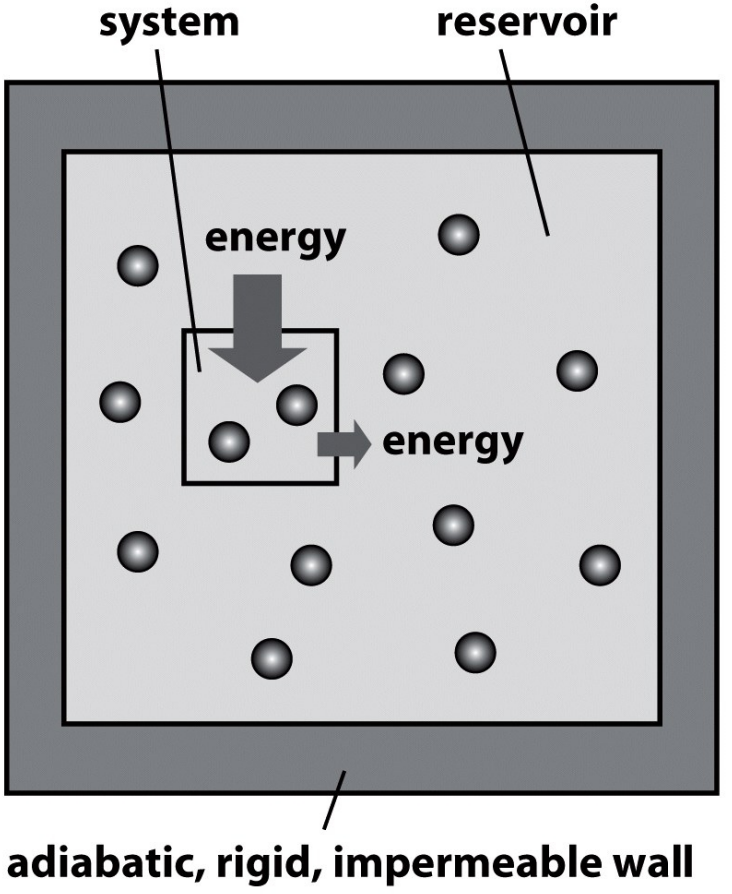


Figure 6.14 Physical Biology of the Cell (© Garland Science 2009)

$$W_{tot}(E_{tot} - E_s^I) = 1 \times W_r(E_{tot} - E_s^I)$$

One state of the system x all possible States of the reservoir

$$S = k_B \ln W$$

$$S_r(E_{tot} - E_s) = S_r(E_{tot}) - (\partial S_r/\partial E)\, E_s$$

$$(\partial S_r/\partial E) = 1/T$$

$$p(E_s^I)/p(E_s^{II}) = \exp(-\beta E_s^I)/\exp(-\beta E_s^{II})$$

Relationship between Z and free energy G:

$$G(X) = -k_B T \ln Z$$

Z includes a sum over all microstates that contribute to the macrtostate X!

(A)

	STATE	WEIGHT
X_1	1	$e^{-\beta\varepsilon_1}$
	2	$e^{-\beta\varepsilon_2}$
	3	$e^{-\beta\varepsilon_3}$
	⋮	⋮
	n_1	$e^{-\beta\varepsilon_{n_1}}$
X_2	n_1+1	$e^{-\beta\varepsilon_{n_1+1}}$
	⋮	⋮
	n_2	$e^{-\beta\varepsilon_{n_2}}$
X_3	n_2+1	$e^{-\beta\varepsilon_{n_2+1}}$
	⋮	⋮
	n_3	$e^{-\beta\varepsilon_{n_3}}$

(B)

STATE	WEIGHT
X_1	$e^{-\beta G(X_1)}$
X_2	$e^{-\beta G(X_2)}$
X_3	$e^{-\beta G(X_3)}$
⋮	⋮

Figure 6.15 Physical Biology of the Cell (© Garland Science 2009)