Lecture 7:
Two-State Systems: From Ion Channels To Cooperative Binding

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Examples of two-state systems: state variable σ

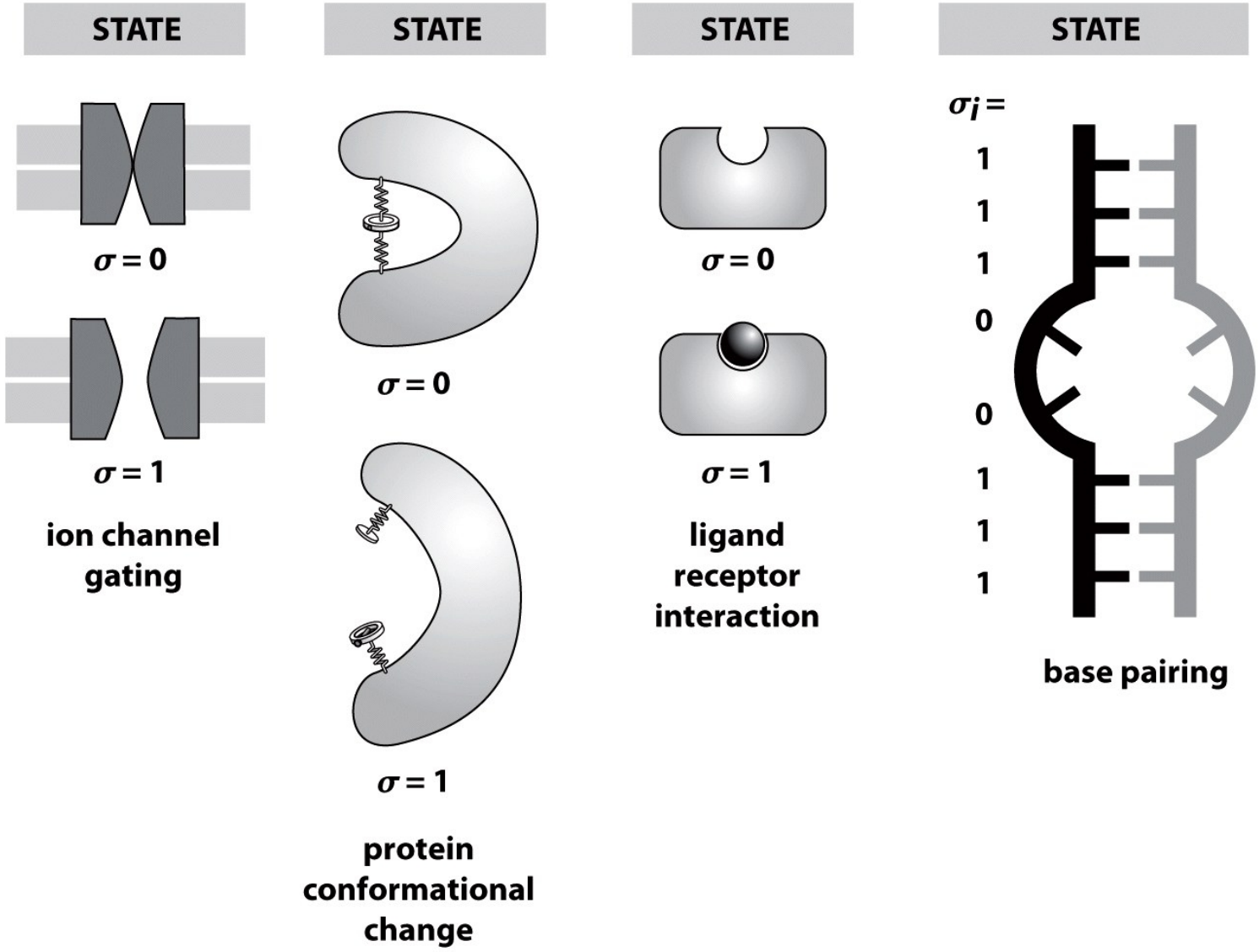


Figure 7.1 Physical Biology of the Cell (© Garland Science 2009)

Current trace and its two state idealization (transition time « dwell time)

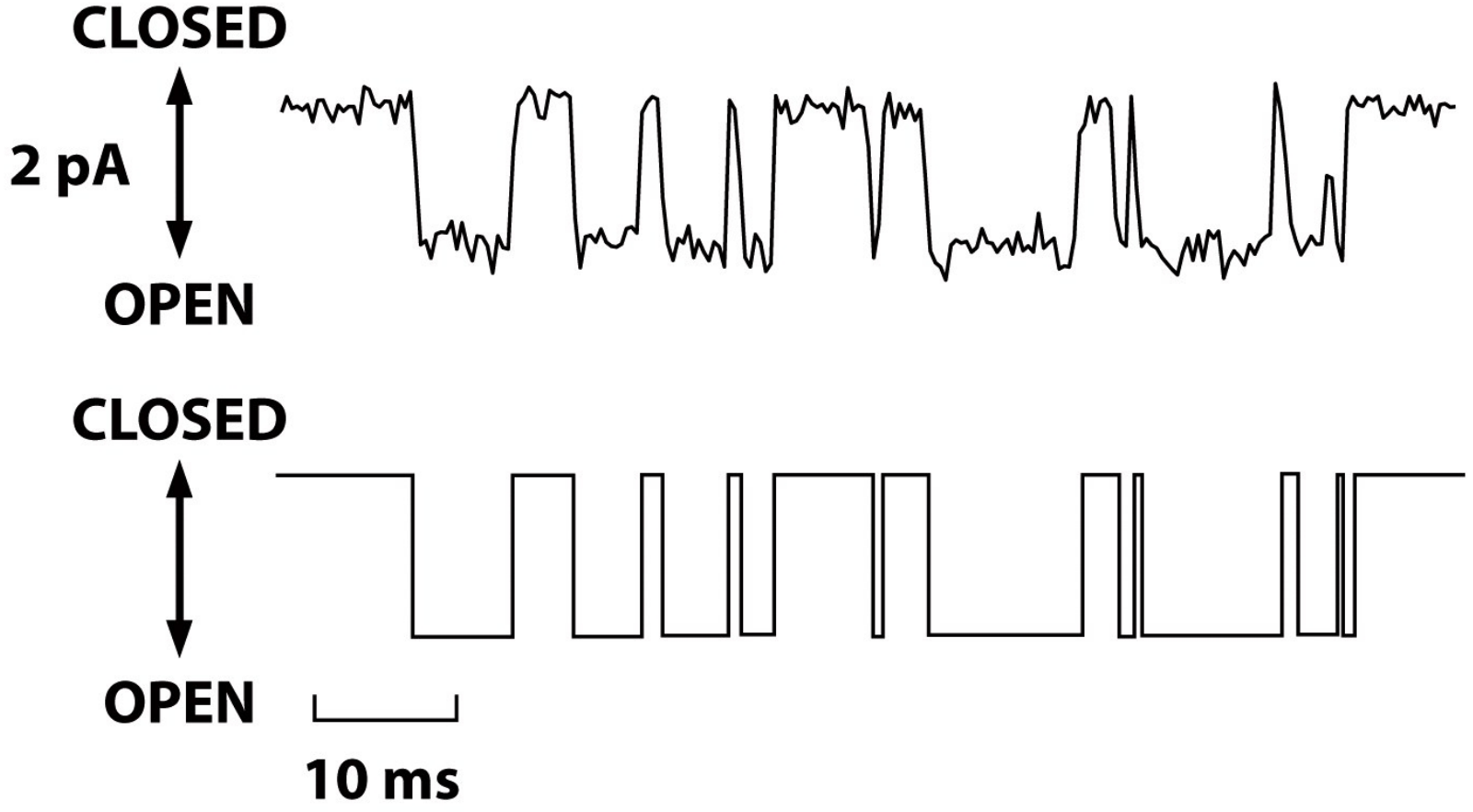
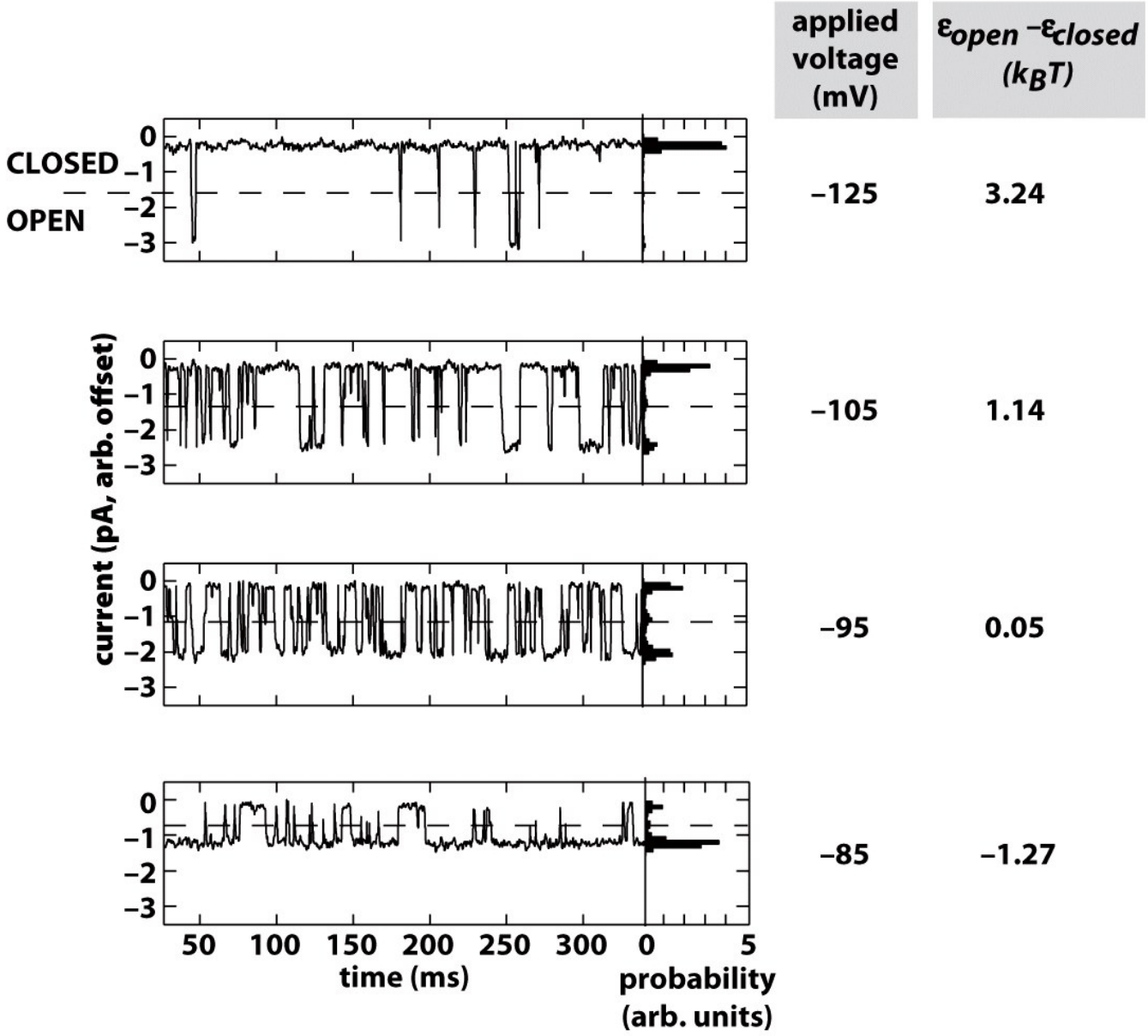


Figure 7.2a Physical Biology of the Cell (© Garland Science 2009)

Ion channels within a lipid Membrane:

Different voltages result in different currents across the membrane



applied voltage (mV)	$\varepsilon_{open} - \varepsilon_{closed}$ (k_BT)
−125	3.24
−105	1.14
−95	0.05
−85	−1.27

Figure 7.2b Physical Biology of the Cell (© Garland Science 2009)

Current proportional to the probability of a channel to be open

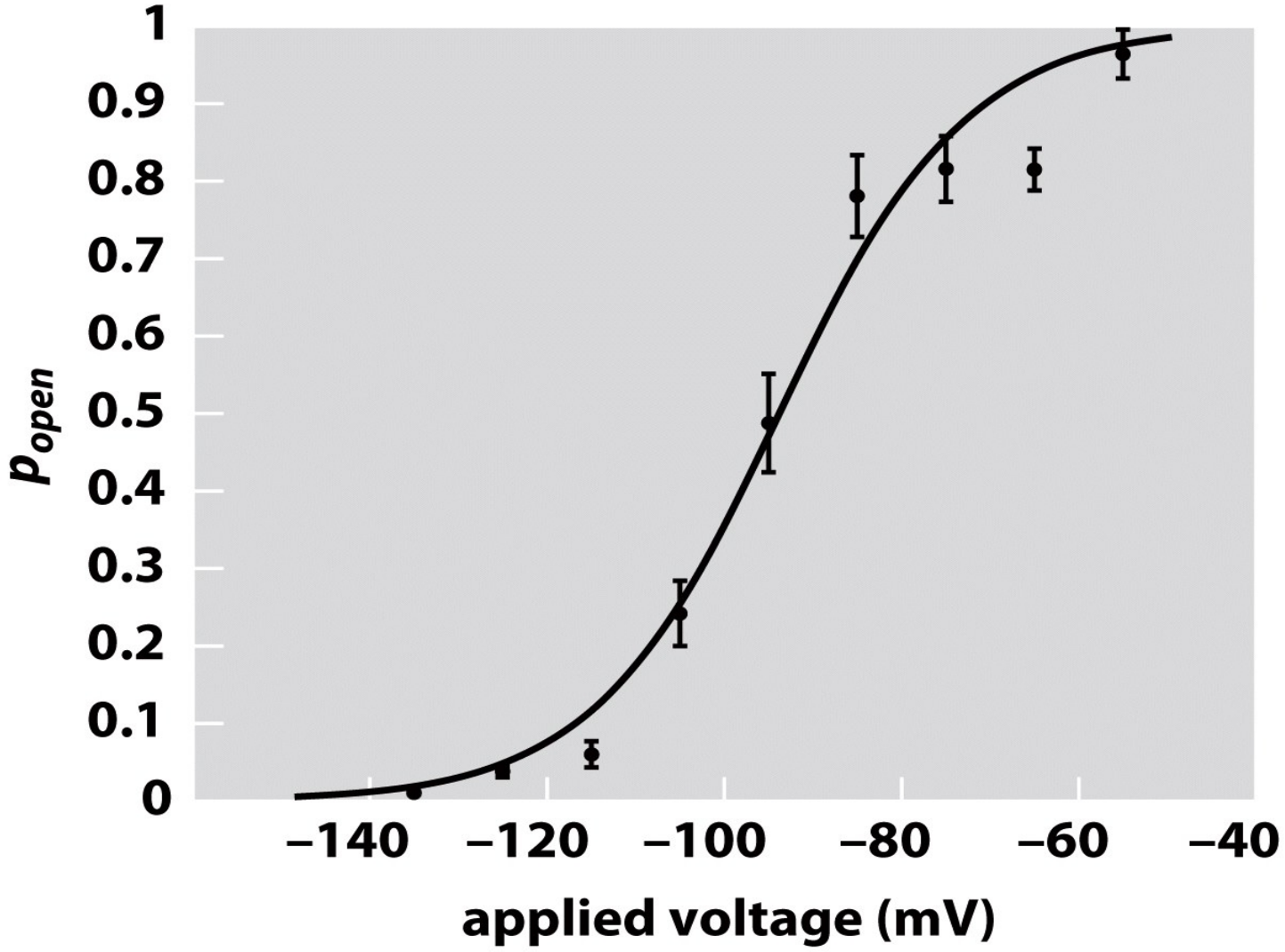


Figure 7.2c Physical Biology of the Cell (© Garland Science 2009)

When the ion channel opens, the energy of the loading device (weights in the figure) decreases (potential energy of weights decreases as the weights are lowered):

weights are a simple representation of externally applied forces

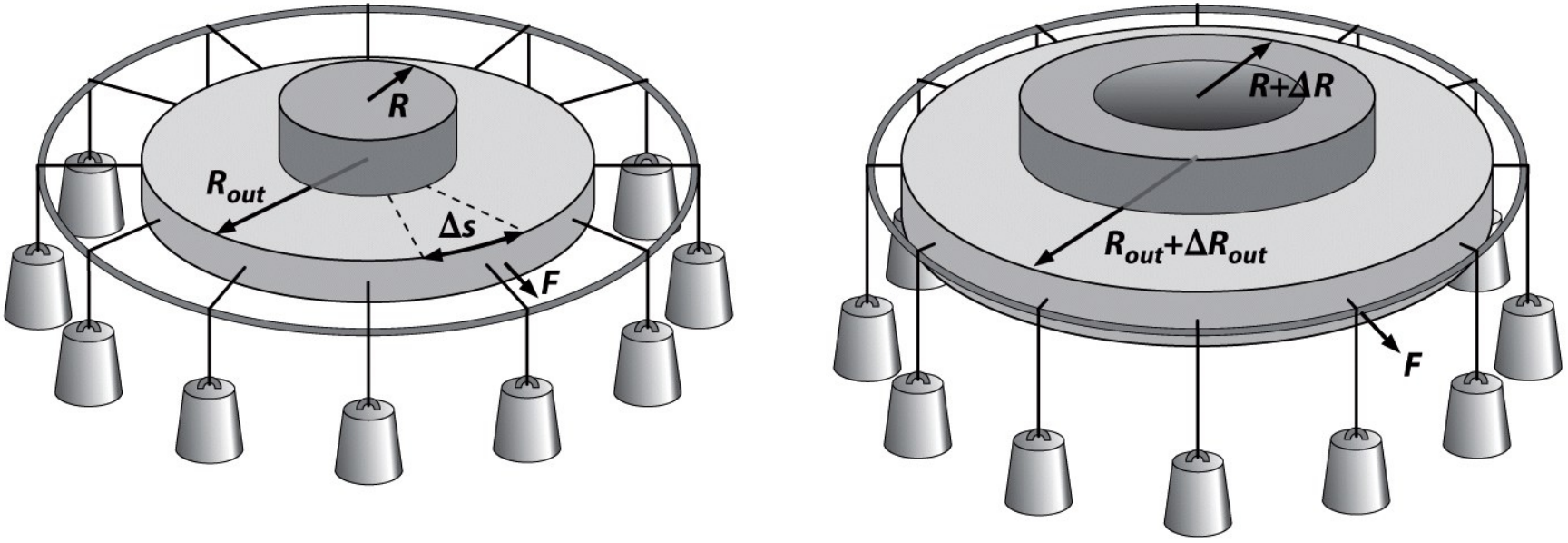


Figure 7.5 Physical Biology of the Cell (© Garland Science 2009)

tension is released

How does the external tension couple to the energy?

$$\Delta G_{TENSION} = -\tau\ \Delta s \times R\,\Delta R/R_{OUT} \times 2\pi R_{OUT}/\Delta s$$

$\tau\ \Delta s$ … force on the arc

$R\Delta R/R_{OUT}$ … the outer radius change (patch displacement)

$2\pi R_{OUT}/\Delta s$ … the number of patches

The outer radius change ΔR_{OUT} follows from the condition that

The membrane area is constant: $\pi R^2_{OUT} - \pi R^2 = \text{const.}$

$$R_{OUT}\,\Delta R_{OUT} - R\Delta R = 0$$

$$\Delta G_{TENSION} = -\tau\ 2\pi\ R\,\Delta R = -\tau\ \Delta A$$

Energy as a function of the internal state variable σ

(σ=1: open σ=0: closed)

No external driving force:

$$E(\sigma) = \sigma\ \varepsilon_{OPEN} + (1-\sigma)\,\varepsilon_{CLOSED}$$

With an external driving force:

$$E(\sigma) = \sigma\ \varepsilon_{OPEN} + (1-\sigma)\,\varepsilon_{CLOSED} - \sigma\tau\Delta A$$

The last term favors an open state!

Two states with the corresponding weights

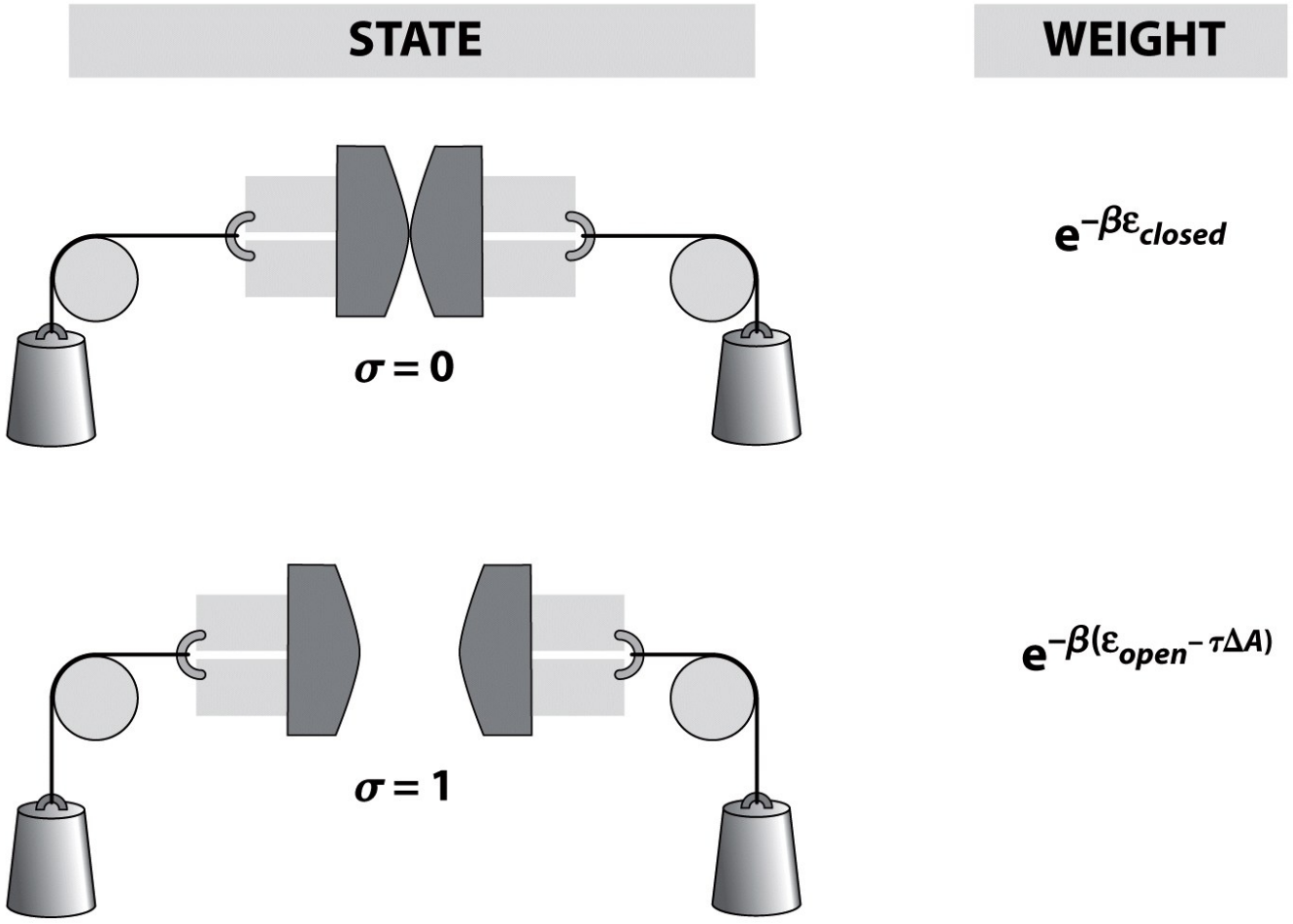


Figure 7.3 Physical Biology of the Cell (© Garland Science 2009)

Energy landscape for an ion channel as a function of radius R for different forces that promote opening

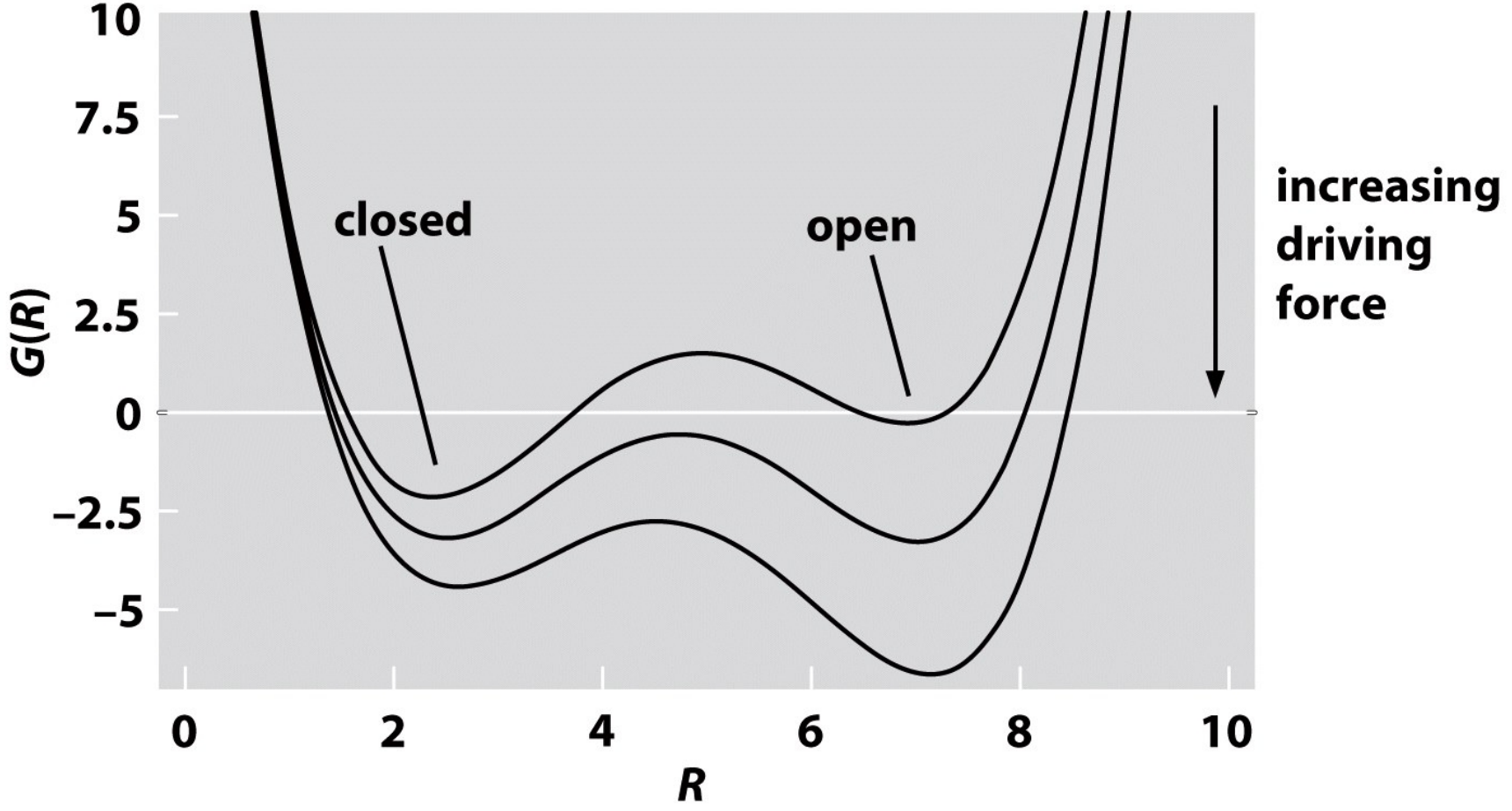


Figure 7.6 Physical Biology of the Cell (© Garland Science 2009)

$$Z = \sum_{\sigma=\{0,1\}} \exp[-\beta E(\sigma)] =$$

$$= \exp[-\beta \varepsilon_{CLOSED}] + \exp[-\beta \varepsilon_{OPEN} + \beta \tau \Delta A]$$

$$\langle \sigma \rangle = p_{OPEN} = p(1) = \exp[-\beta \varepsilon_{OPEN} + \beta \tau \Delta A]/Z$$

Ion channel opening probability as a function of driving force for gating (membrane tension τ)

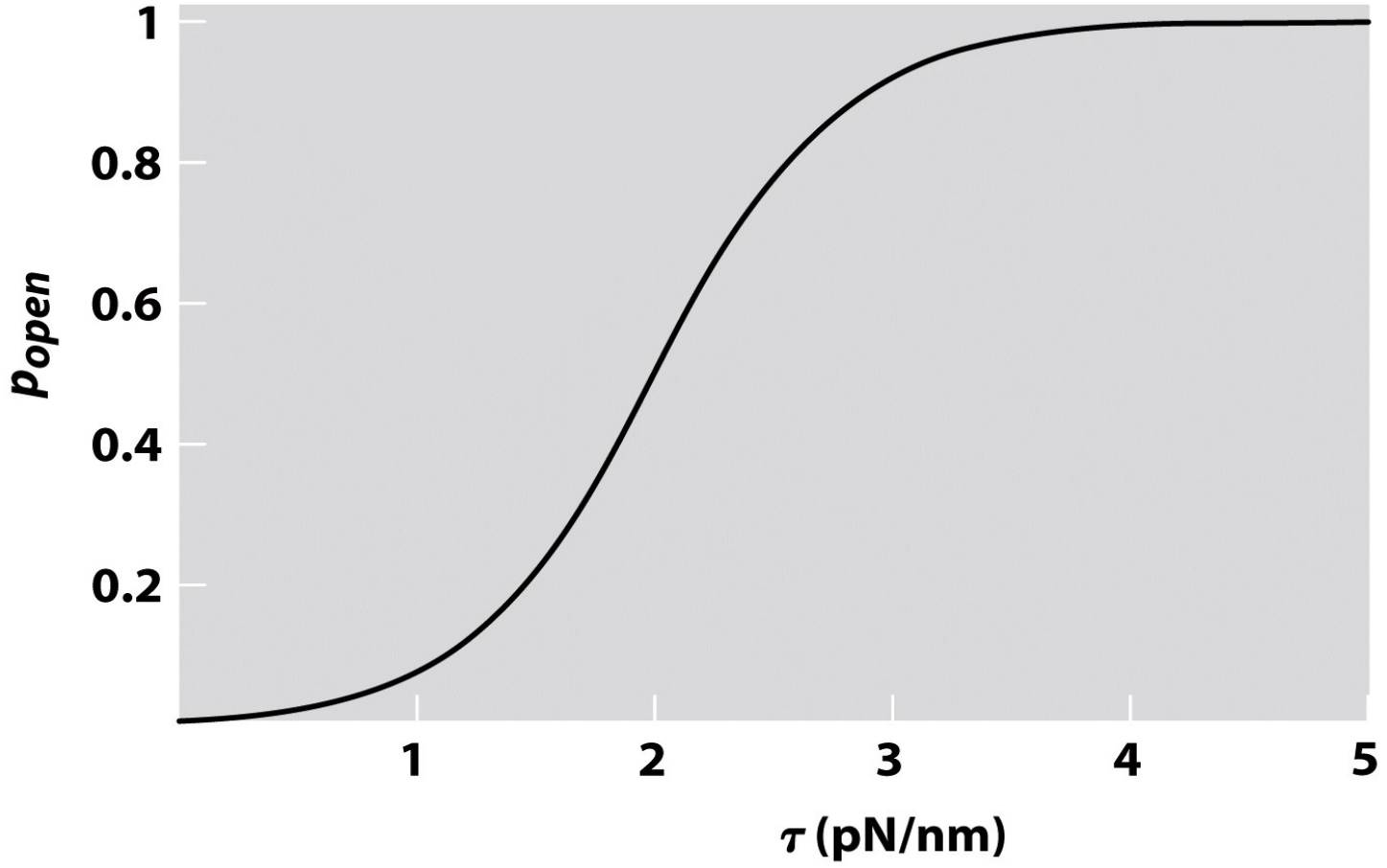


Figure 7.7 Physical Biology of the Cell (© Garland Science 2009)

State variable description of binding: Grand partition function and Gibbs distribution

Open system exchanges both energy and particles with the reservoir.

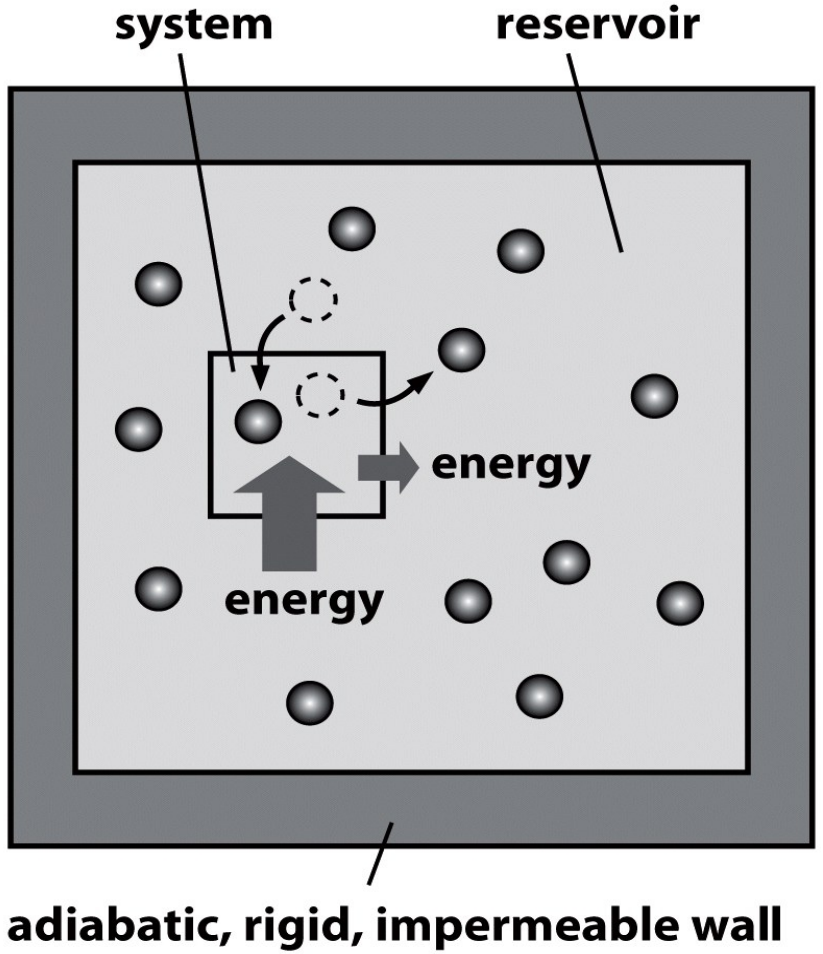


Figure 7.8 Physical Biology of the Cell (© Garland Science 2009)

We apply the same principle of maximal entropy to the isolated "universe" of the system and the reservoir:

$$W_{TOT}(E_{TOT} - E_S, N_{TOT} - E_S) = 1 \times W_R(E_{TOT} - E_S, N_{TOT} - N_S)$$

Such that the ratio of the probabilities to find the system in microstates I and II can be expressed as:

$$p(E_S^I, N_S^I) / p(E_S^{II}, N_S^{II}) =$$

$$W_R(E_{TOT} - E_S^I, N_{TOT} - N_S^I) / W_R(E_{TOT} - E_S^{II}, N_{TOT} - N_S^{II})$$

Because $S = k_B \ln W$, the above ratio can be expressed as:

$$W_R(E_{TOT} - E_S^I, N_{TOT} - N_S^I) / W_R(E_{TOT} - E_S^{II}, N_{TOT} - N_S^{II}) =$$

$$\exp[S_R(E_{TOT} - E_S^I, N_{TOT} - N_S^I)/k_B] / \exp[S_R(E_{TOT} - E_S^{II}, N_{TOT} - N_S^{II})/k_B]$$

$$S_R(E_{TOT} - E_S, N_{TOT} - N_S) = S_R(E_{TOT}) - (\partial S_R/\partial E)\, E_S - (\partial S_R/\partial N)\, N_S = S_R(E_{TOT}) - E_S/T + \mu N_S/T$$

$$(\partial S_R/\partial E) = 1/T \quad \text{and} \quad (\partial S_R/\partial N) = -\mu/T$$

Thus, we find:

$$p(E_S^I, N_S^I)\,/\,p(E_S^{II}, N_S^{II}) =$$

$$= \exp[-\beta(E_S^I - \mu N_S^I)]/\exp[-\beta(E_S^{II} - \mu N_S^{II})]$$

We derived the Gibbs distribution:

$$p(E_S^i, N_S^i) = \exp[-\beta(E_S^i - \mu N_S^i)]/Z$$

$$Z = \sum \exp[-\beta(E_S^i - \mu N_S^i)] \ldots \text{grand partition function}$$

Simple Ligand-Receptor Binding through Gibbs distribution

$Z = 1 + \exp[-\beta(\varepsilon_b - \mu)]$ … grand partition function

$p_b = \langle N \rangle = \beta^{-1} \partial \ln Z / \partial \mu$

$= \exp[-\beta(\varepsilon_b - \mu)]/Z$

$\mu = \mu_0 + \beta^{-1} \ln(c/c_0)$

$p_b = \langle N \rangle =$

$c/c_0 \exp(-\beta\Delta\varepsilon)/[1 + c/c_0 \exp(-\beta\Delta\varepsilon)]$

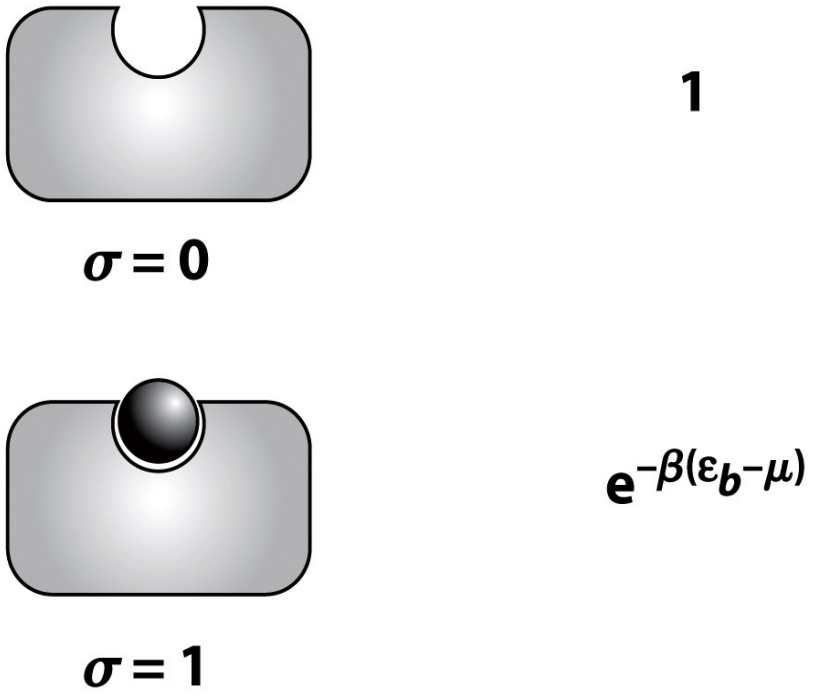


Figure 7.9 Physical Biology of the Cell (© Garland Science 2009)

Phosphorylation

(covalent post-translational modification)

Attachment of phosphate groups to specific substrates:

-in proteins within eukaryotic cells amino acids with hydroxyl groups (serine, threonine, and tyrosine), added a phosphate group with two negative charges

-ATP

-kinase enzymes assist in phosphorylation

-reversed process facilitated by another type of enzymes: phosphatases (use water to hydrolyze the bonds)

-controls protein activity (in response to environmental changes)

Example of a two state description:

$\sigma_S = 1$ … active

$\sigma_S = 0$ … inactive

$\sigma_P = 1$ … phosphorylated

$\sigma_P = 0$ … unphosphorylated

phosphorylation lowers the energy of both states but more the active state

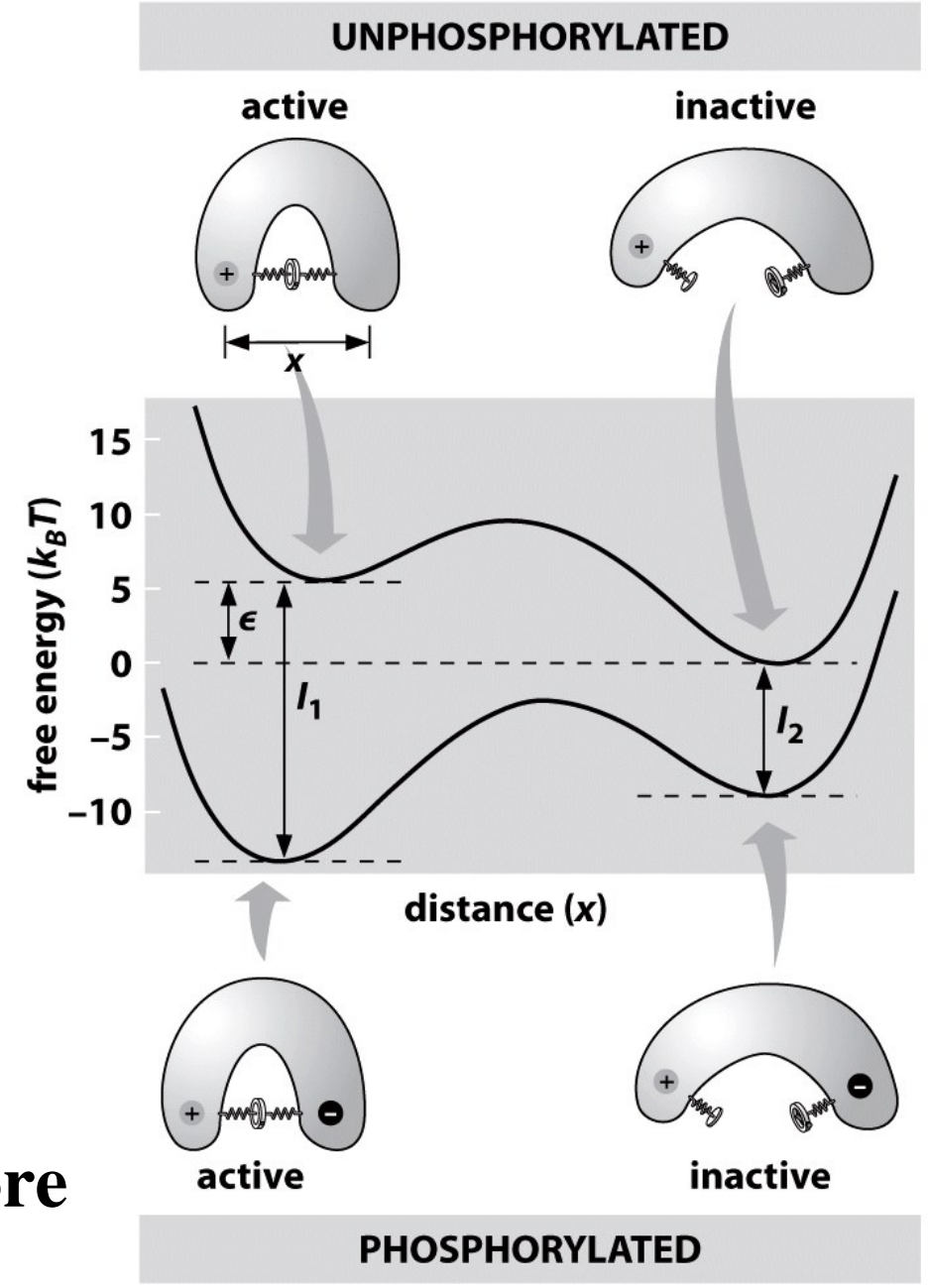


Figure 7.10 Physical Biology of the Cell (© Garland Science 2009)

Free energy of the protein:

$$G(\sigma_P, \sigma_S) =$$
$$(1-\sigma_P)\,[(1-\sigma_S)\,0 + \varepsilon\sigma_S]$$
$$+\ \sigma_P[(1-\sigma_S)\,(-I_2) + \sigma_S(\varepsilon - I_1)]$$
$$= \varepsilon\sigma_S - I_2\sigma_P + (I_2 - I_1)\,\sigma_S\,\sigma_P$$

$$-p_A = \exp(-\beta\varepsilon)/[1+\exp(-\beta\varepsilon)]$$

for unphosphorylated case

$$-\ p_A^* = B/(B+C) \gg p_A$$

for phosphorylated case

$$B = \exp[-\beta(\varepsilon - I_1)]\ \&\ C = \exp(\beta I_2)$$

factor of 2 up to 1,000 fold increase in activity upon phosphorylation

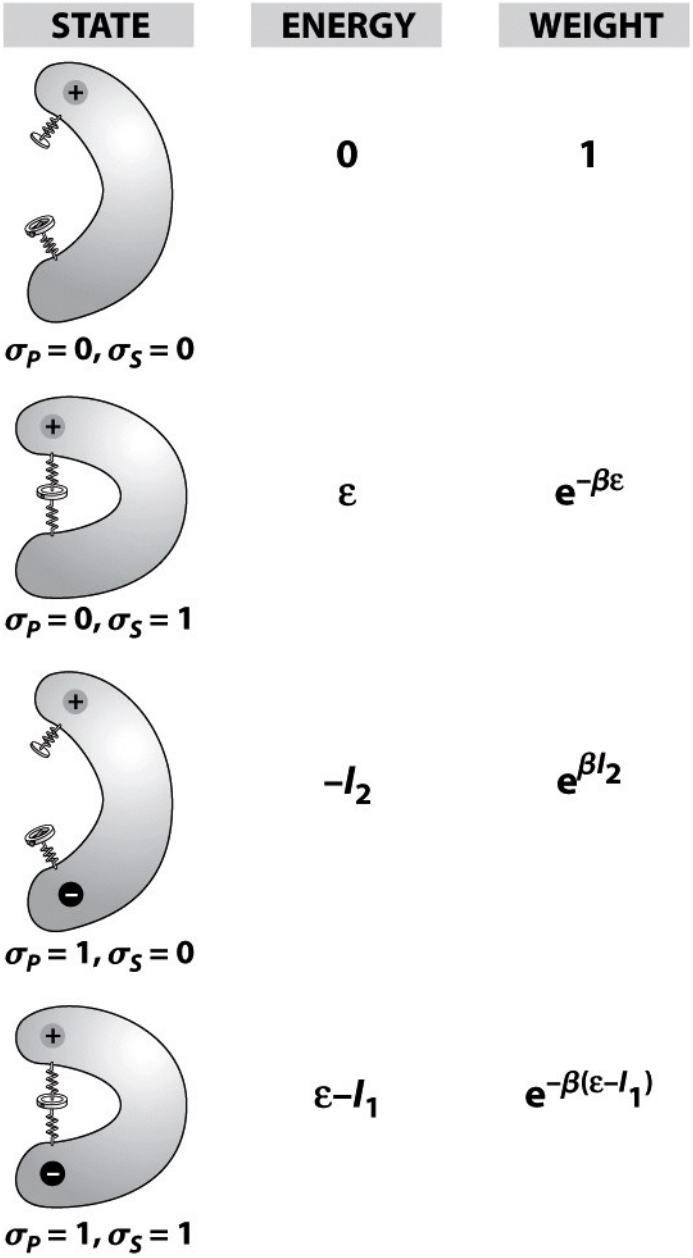


Figure 7.11 Physical Biology of the Cell (© Garland Science 2009)

Oxygen binding in hemoglobin

- ***4 oxygen binding sites*** **in each hemoglobin molecule**
- ***cooperativity*****: binding energy of each oxygen depends on the number of oxygens that are already bound to hemoglobin**
- **biophysical basis: each bound O: conformational change that makes it easier for other Os to bind**
- **toy model of dimeric hemoglobin (O_2)**

dimoglobin **binding**

$$E = \varepsilon(\sigma_1 + \sigma_2) + J\sigma_1\sigma_2$$

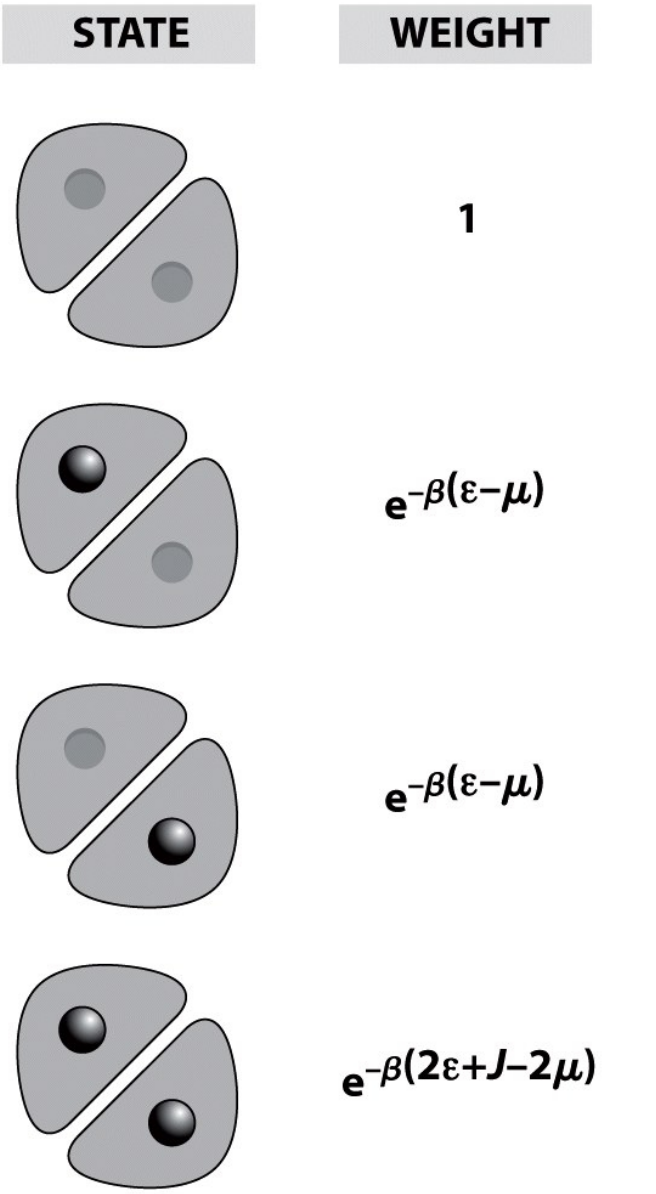


Figure 7.12 Physical Biology of the Cell (© Garland Science 2009)

Grand partition function:

$$Z = 1 + 2\exp[-\beta(\varepsilon-\mu)] + \exp[-\beta(2\varepsilon-2\mu+J)] \ldots (p_0, p_1, p_2)$$

$$p_0 = 1/Z;\ p_1 = 2\exp[-\beta(\varepsilon-\mu)]/Z;\ p_2 = \exp[-\beta(2\varepsilon-2\mu+J)/Z$$

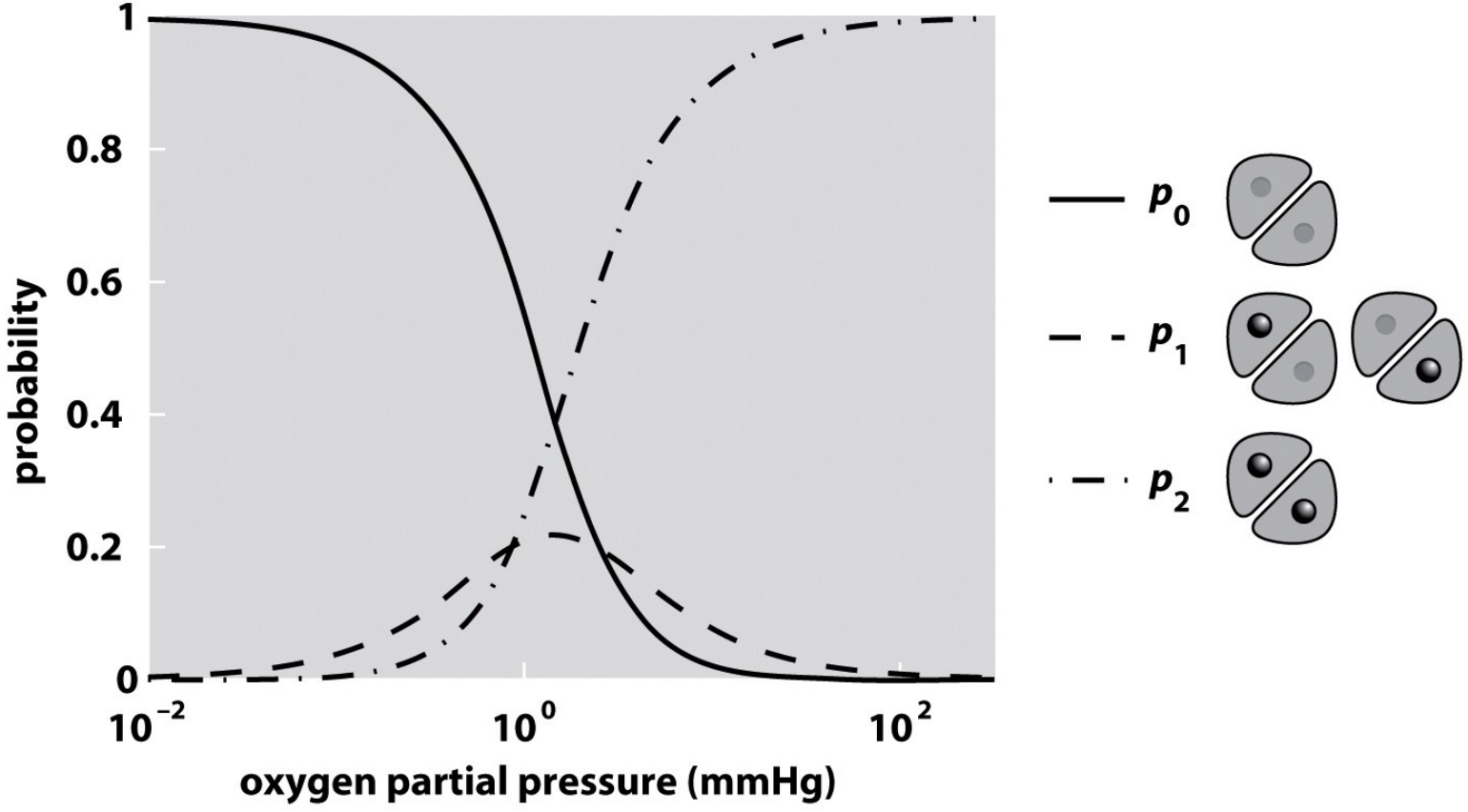


Figure 7.13 Physical Biology of the Cell (© Garland Science 2009)

$$\mu = \mu_0 + k_B T \ln(c/c_0);\ \Delta\varepsilon = \varepsilon - \mu_0;\ x = c/c_0;$$

$$\langle N \rangle = A/(1+A);\ A = 2x \exp(-\beta\Delta\varepsilon) + 2x^2 \exp[-\beta(2\Delta\varepsilon + J)]$$

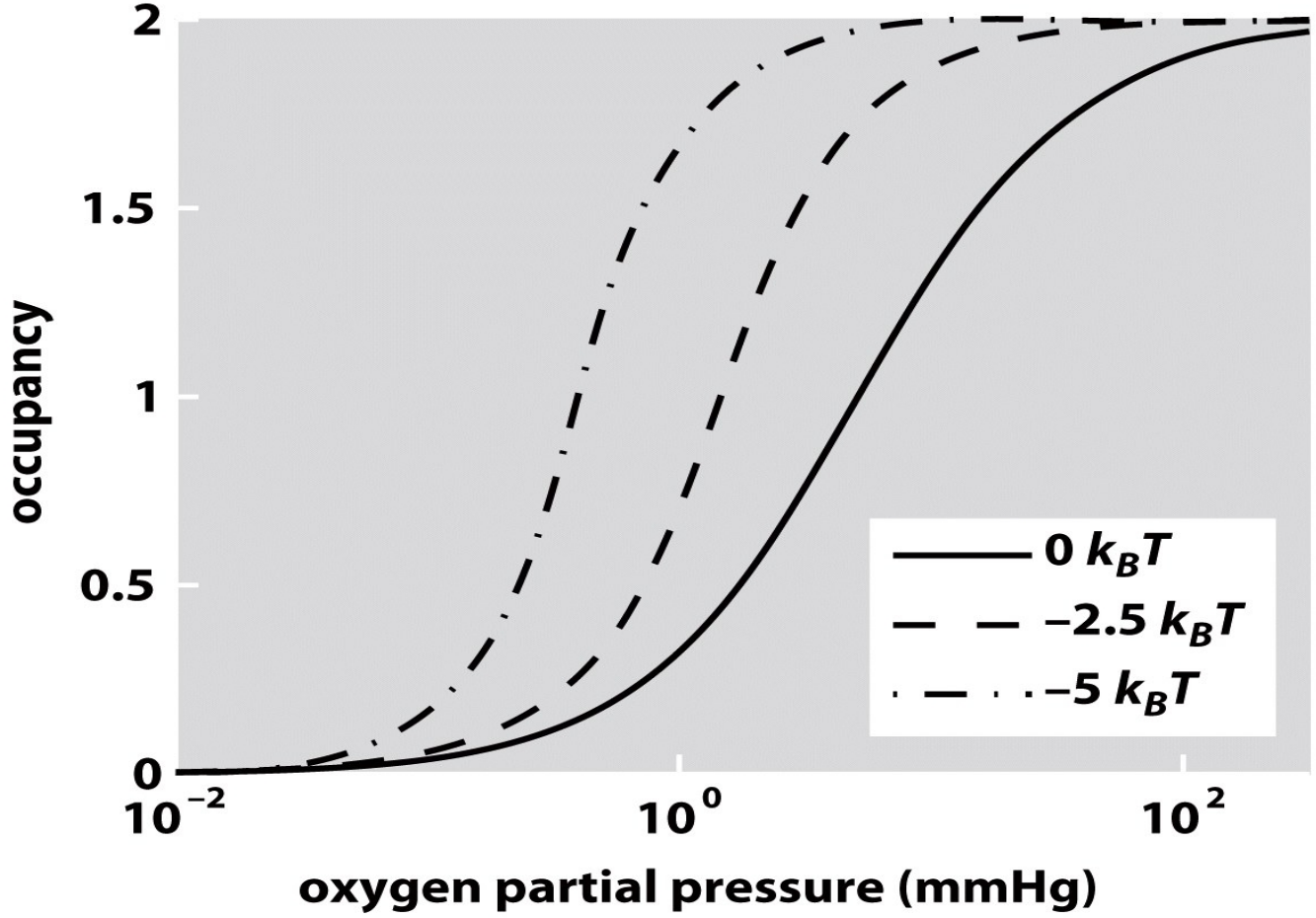


Figure 7.14 Physical Biology of the Cell (© Garland Science 2009)

The Monod-Wyman-Changeux (MWC) Model of Cooperative Binding

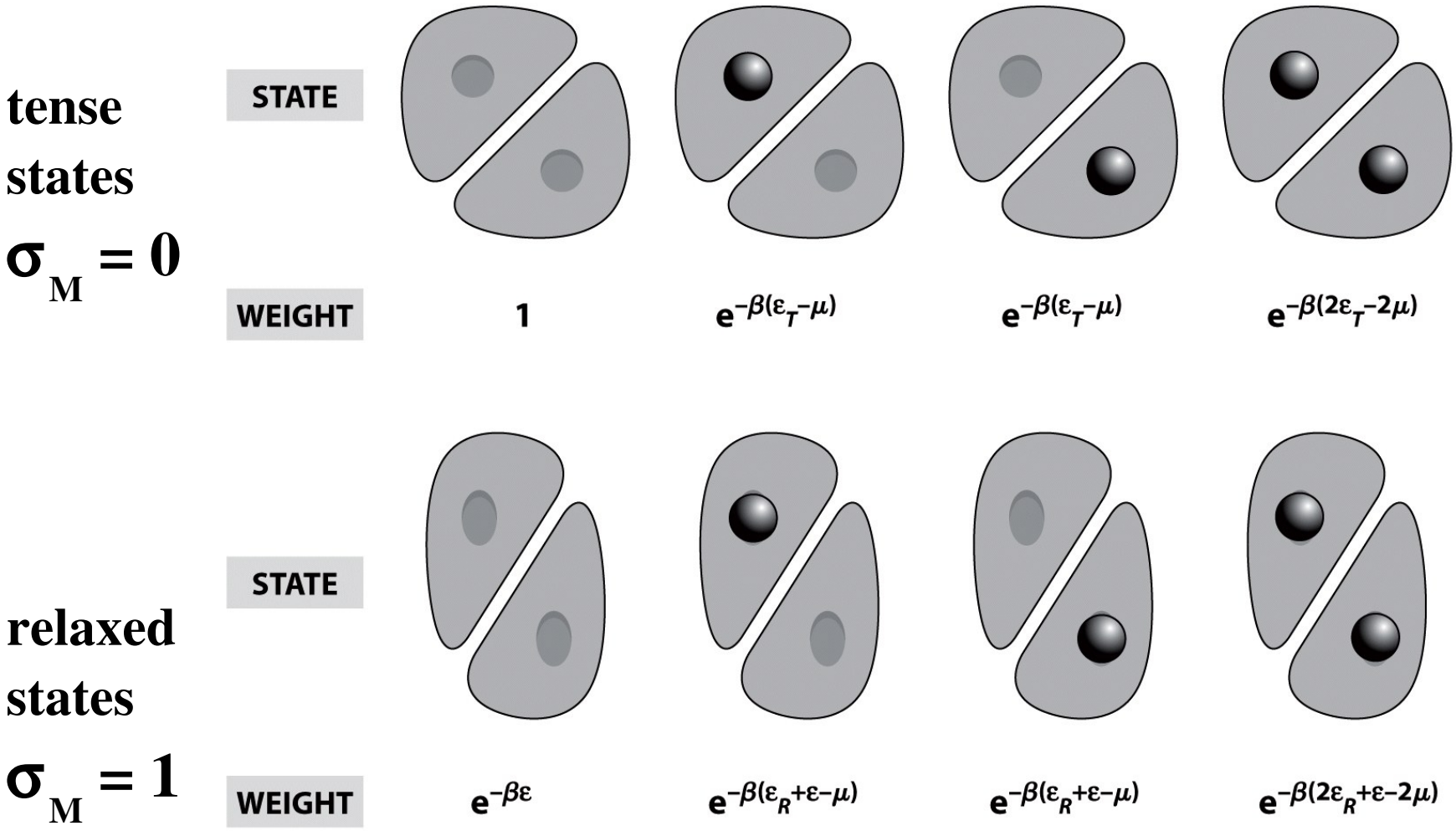


Figure 7.15 Physical Biology of the Cell (© Garland Science 2009)

Description of the MWC model of oxygen binding in dimoglobin:

- a classic two-state model for binding
- protein can exist in two distinct states: T (tense) and R (relaxed)
- T is favored over R: $\varepsilon_T < \varepsilon_R$ so that $\varepsilon = \varepsilon_R - \varepsilon_T > 0$
- the first two-state variable: $\sigma_M = 0$ (Tense), $\sigma_M = 1$ (Relaxed)
- the second two-state variable: $\sigma_i = 0$ (empty), $\sigma_i = 1$ (occupied)
- the variable $i \in \{1, 2\}$ corresponds to the receptor place in dimoglobin (two sites of binding)
- complete energy E:

$$E = (1 - \sigma_M)\, \varepsilon_T \sum_i \sigma_i + \sigma_M (\varepsilon + \varepsilon_R \sum_i \sigma_i)$$

Tense Part + Relaxed Part

$$Z = 1 + \exp[-\beta(\varepsilon_T - \mu)] + \exp[-\beta(2\varepsilon_T - 2\mu)] + \exp(-\beta\varepsilon) \times$$
$$\{1 + \exp[-\beta(\varepsilon_R - \mu)] + \exp[-\beta(2\varepsilon_R - 2\mu)]\}$$

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

$$\langle N \rangle = 2/Z \times$$
$$[x + x^2 + \exp(-\beta\varepsilon)$$
$$(y + y^2)]$$

$$x = c/c_0 \exp[-\beta(\varepsilon_T - \mu_0)]$$
$$y = c/c_0 \exp[-\beta(\varepsilon_R - \mu_0)]$$

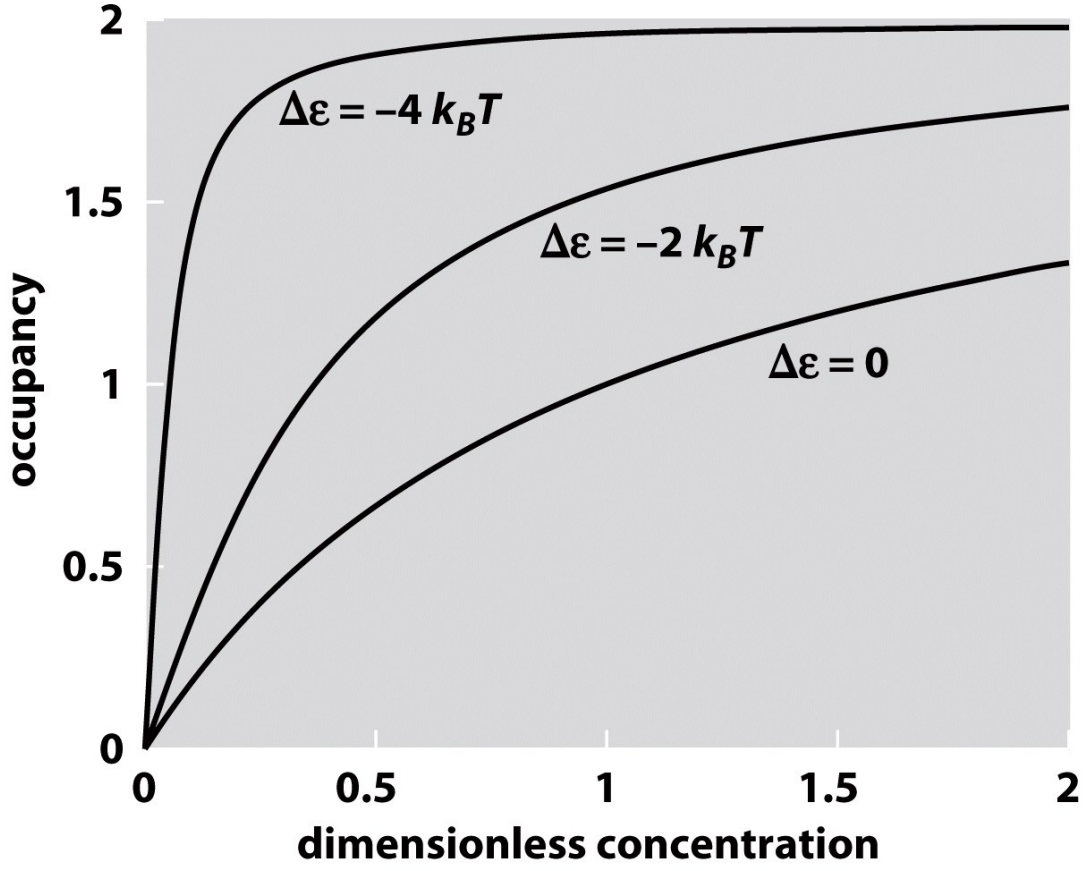


Figure 7.16 Physical Biology of the Cell (© Garland Science 2009)

Increasingly Complex Binding Models for Hemoglobin

(1) ***Noncooperative Model*****:**

- binding on the 4 sites of hemoglobin independent

- energy: $E = \varepsilon \sum_i \sigma_i \quad i \in \{1,2,3,4\}$

(2) ***Pauling Model*****:**

- four sites as vertices of a tetrahedron

- binding to the neighboring sites is favorable

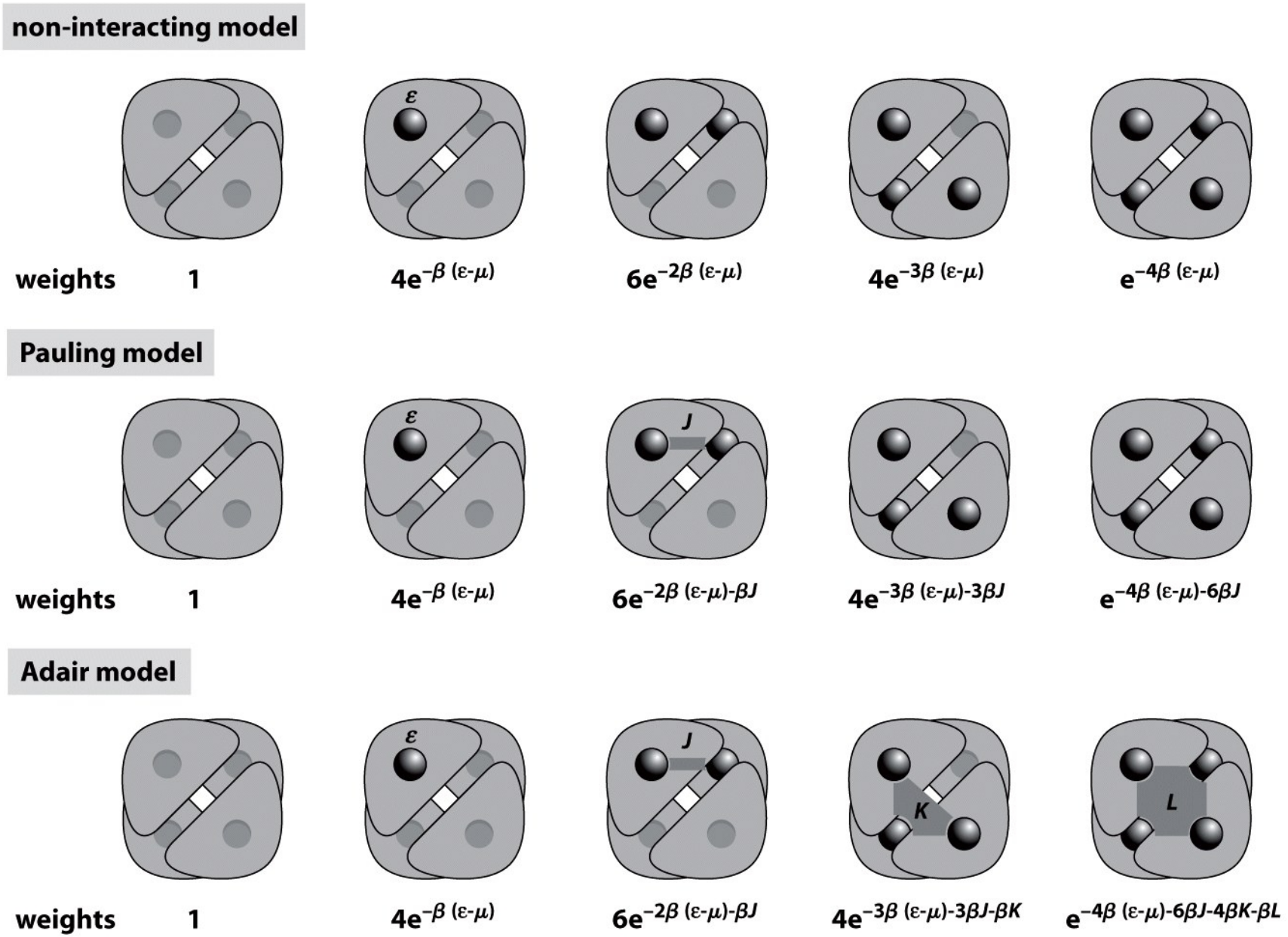
- energy: $E = \varepsilon \sum_i \sigma_i + J/2 \sum'_{ij} \sigma_i \sigma_j \quad i,j \in \{1,2,3,4\}$

(3) ***Adair Model*****:**

- in addition to cooperativity of the Pauling model accounts for three- and four-body interactions

- energy E:

$$E = \varepsilon \sum_i \sigma_i + J/2! \sum'_{ij} \sigma_i \sigma_j + K/3! \sum'_{ijk} \sigma_i \sigma_j \sigma_k + L/4! \sum'_{ijkl} \sigma_i \sigma_j \sigma_k \sigma_l$$



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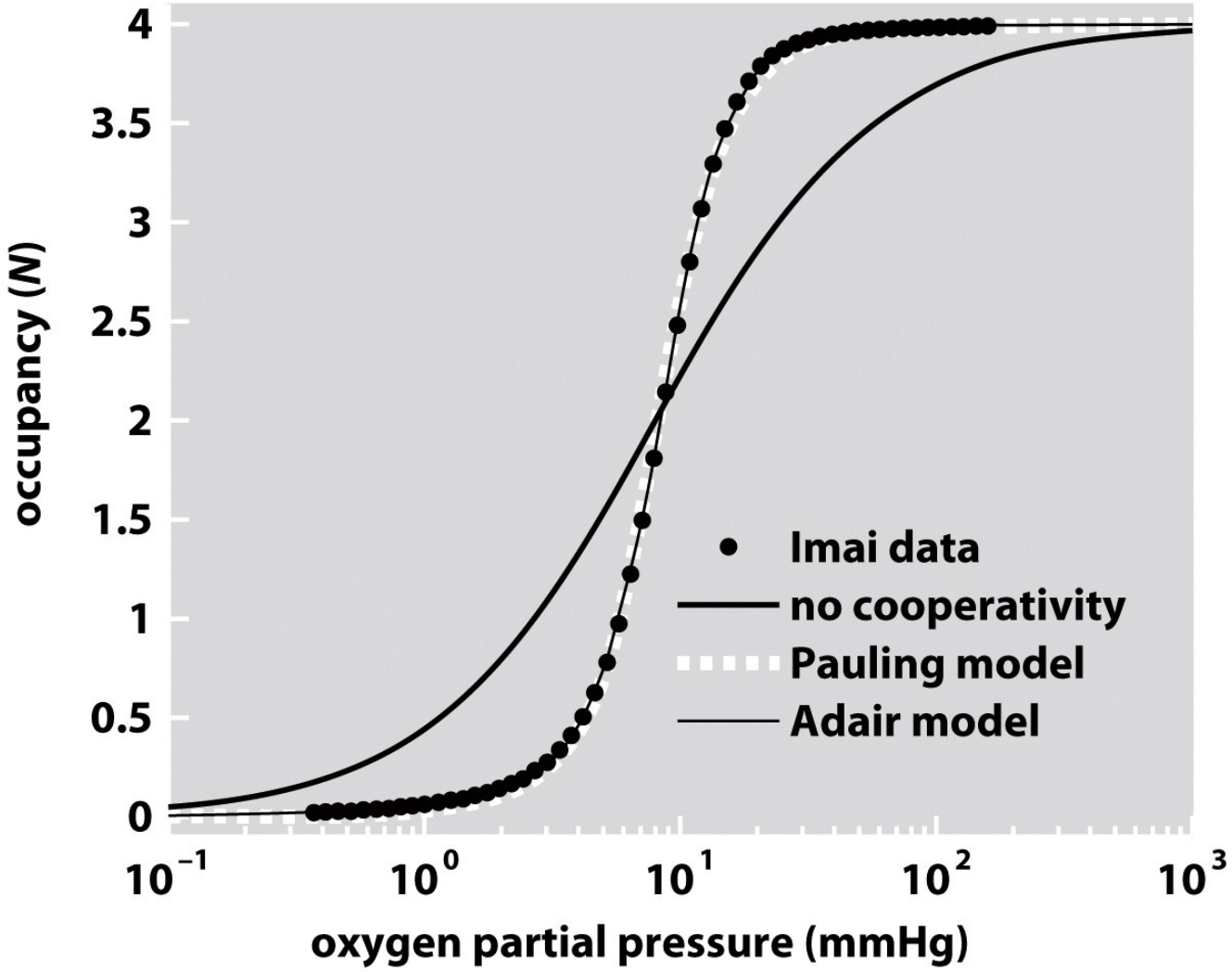
Cooperative binding associated with a sharper transition



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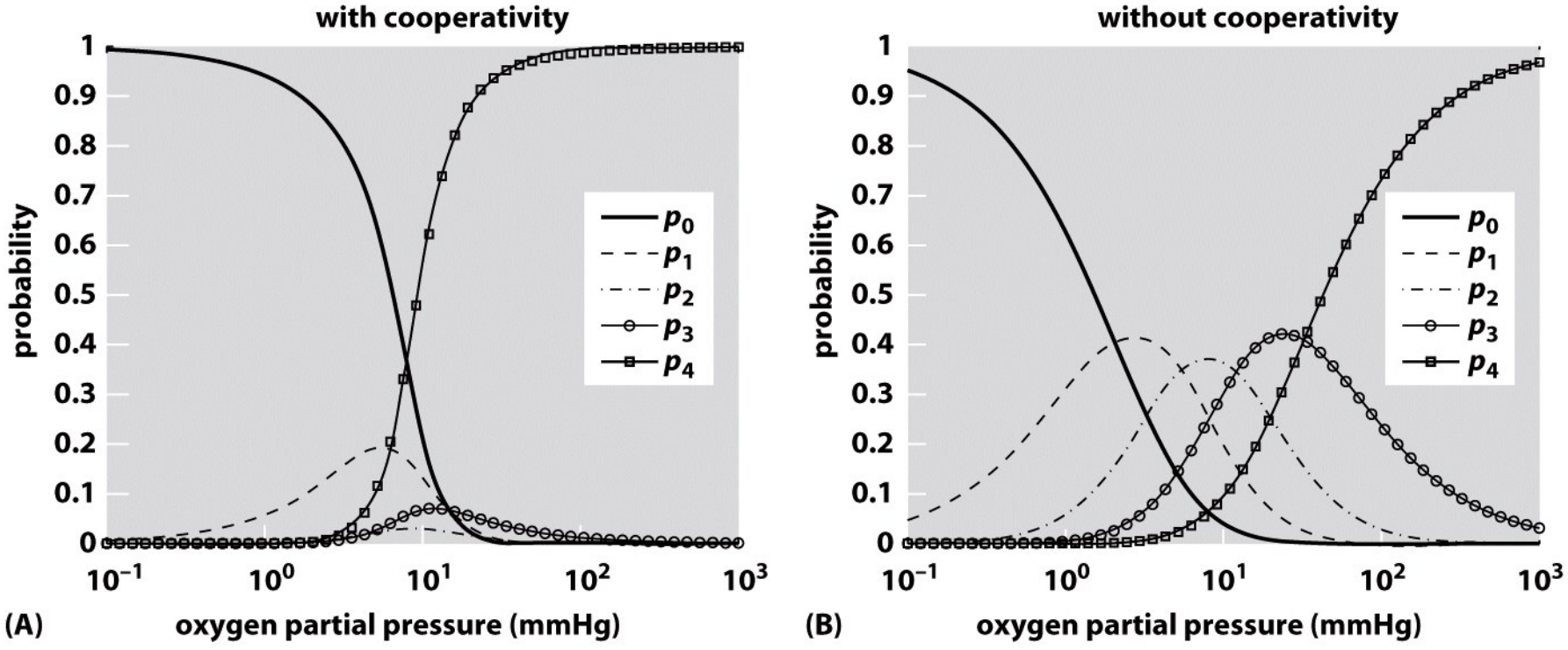
Cooperative binding eliminates the intermediate states (1, 2, or 3 oxygens bound to hemoglobin: all-or-none behavior)



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