Lecture 4. Preliminary and simple applications of statistical mechanics

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Main contents

- Fundamental concepts and equations
- Simple applications: ligand-receptor binding and gene expression
- Two-state model
- Cooperative binding of Hemoglobin
- RNA folding and unfolding

§ 4.1 Fundamental concepts & equations

Conventional thermodynamics

- Object
  - Systems: large number of particles (~10^{23})
  - Short-range interaction between particles (ideal gas, vdW gas, plasma, polymer; ~~gravity~~ system, + or - ~~charged~~ system)

    Interaction potential $< r^{-3}$, for $r \to \infty$
  - An isolated system can reach thermal equilibrium through long enough but finite-time relaxation

- Four thermodynamic laws
  - 0th: it is possible to build a thermometer
  - 1st: energy is conserved $\mathrm{d}U = \bar{d}Q + \bar{d}W_k$
  - 2nd: not all heat can be converted into work

$$dS \geqslant \bar{d}\,Q/T$$

  - 3rd: 0K cannot be reached via finite reversible steps

Note in thermodynamics:

Entropy can be defined as $dS \geqslant \bar{d}\,Q/T$ via reversible process

- Free energy (Helmholtz)

$$F = U - TS$$

1st+2nd+const. T: $dS \geqslant \bar{d}Q/T$

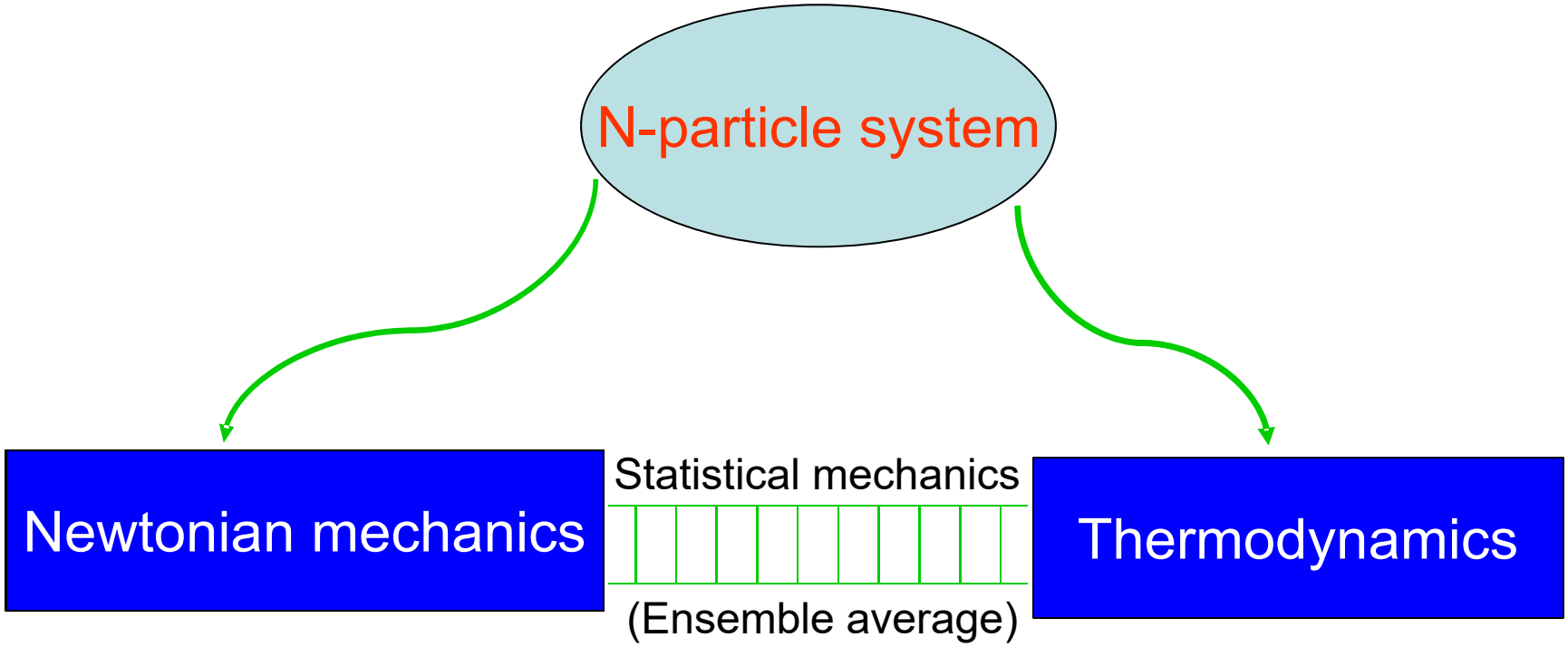
$$dF = dU - TdS = \bar{d}W_k + \bar{d}Q - TdS \leq \bar{d}W_k$$

$$-\bar{d}W_k \leq -dF$$

Free energy change = maximum work done by the system on the outer environment in isothermal process

Statistical mechanics

- Function



A bridge from microscopic motions of a large number of molecules to macroscopic behavior of the system consisting of these molecules.

More is different 多者异也

Philip W. Anderson(1923－)，1977 Nobel Prize

4 August 1972, Volume 177, Number 4047 SCIENCE

More Is Different

Broken symmetry and the nature of the hierarchical structure of science.

P. W. Anderson

The reductionist hypothesis may still be a topic for controversy among philosophers, but among the great majority of active scientists I think it is accepted

planation of phenomena in terms of known fundamental laws. As always, distinctions of this kind are not unambiguous, but they are clear in most cases. Solid state physics, plasma physics, and perhaps

less relevance they seem to have to the very real problems of the rest of science, much less to those of society.

The constructionist hypothesis breaks down when confronted with the twin difficulties of scale and complexity. The behavior of large and complex aggregates of elementary particles, it turns out, is not to be understood in terms of a simple extrapolation of the properties of a few particles. Instead, at each level of complexity entirely new properties appear, and the understanding of the new behaviors requires research which I think is as fundamental in its nature as any other. That is, it seems to me that one may array the sciences roughly linearly in a hierarchy, according to the idea: The elementary entities of science X obey the laws of science Y.

Statistical physics in understanding living systems

The physics of life

From flocking birds to swarming molecules, physicists are seeking to understand 'active matter' — and looking for a fundamental theory of the living world.

BY GABRIEL POPKIN

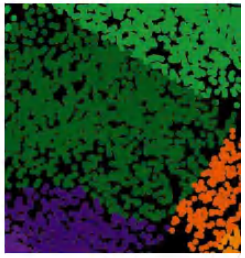
Nature 2016

nature physics

Search

INSIGHT | 04 JULY 2018

Physics of living systems



Recent advances in our understanding of the physics of living systems have come from biologists and physicists working in close collaboration. This Insight celebrates this approach by showcasing research across all the length scales relevant to living systems — from molecules and cells to tissues, organisms and populations. show less

Editorial

EDITORIAL
4 JUL 2018
Nature Physics

Physics of living systems
Abigail Klopper

Reviews & Comment

COMMENT
4 JUL 2018
Nature Physics

Biophysics across time and space
Understanding the behaviour of almost any biological object is a fundamentally multiscale problem — a challenge that biophysicists have been increasingly embracing, building on two centuries of biophysical studies at a variety of length scales.
Ewa K. Paluch

REVIEW ARTICLE
4 JUL 2018
Nature Physics

Physical biology of the cancer cell glycocalyx
It may look like little more than slime, but the glycocalyx coating our cells plays a key role in cell signalling. And changes to its physical structure have been linked to cancer, triggering emergent behaviours that form the focus of this Review.
Joe Chin-Hun Kuo, Jay G. Gandhi ··· Matthew J. Paszek

PERSPECTIVE
4 JUL 2018
Nature Physics

In pursuit of the mechanics that shape cell surfaces
Robust and responsive, the surface of a cell is as important as its interior when it comes to mechanically regulating form and function. New techniques are shedding light on this role, and a

This is evident in the fact that a cell's shape, mechanics or signalling behaviour cannot be divined from nanoscale dynamics in the molecularly crowded environment of the cell surface[9,10]. Similarly, although tissue behaviour is controlled by cell dynamics and interactions, it cannot be directly predicted from cellular properties or from the molecular principles that control them[11]. The same problem exists at a higher scale, in investigations of collective behaviour in groups of animals[12].

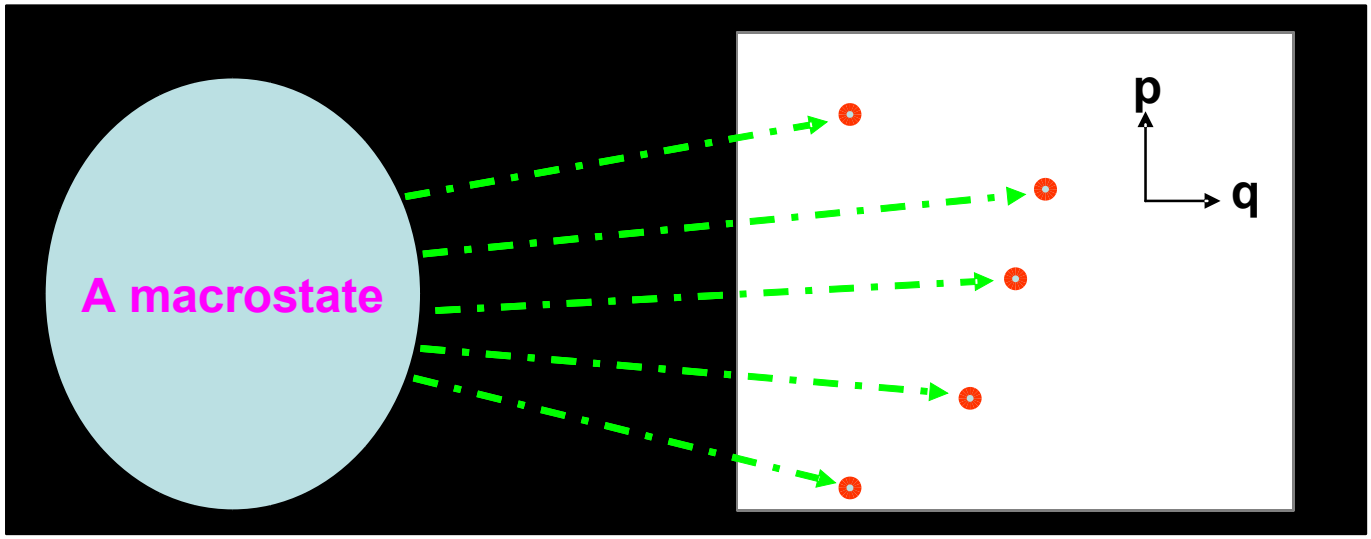
Tools from statistical physics have been invaluable in providing a conceptual framework to understand emergent multiscale properties in biology[9,11,12]. Emergent behaviours in a complex system can often be described in the form of phase diagrams, as a function of variables capturing specific properties of the system components[11]. Such approaches are powerful because they help identify key mesoscale principles governing the collective behaviour. Transitions in behaviour — be it a cell's state, the shape of a tissue or the directional polarization of a group of ants — can then be described in the rich physical framework of phase transitions.

Phase diagram/transition

Macrostate: thermodynamic EQ state

- e.g. PVT

Microstate: phase point (q,p)



Each macrostate corresponds to many microstates!
Each microstate occurs at some probability.

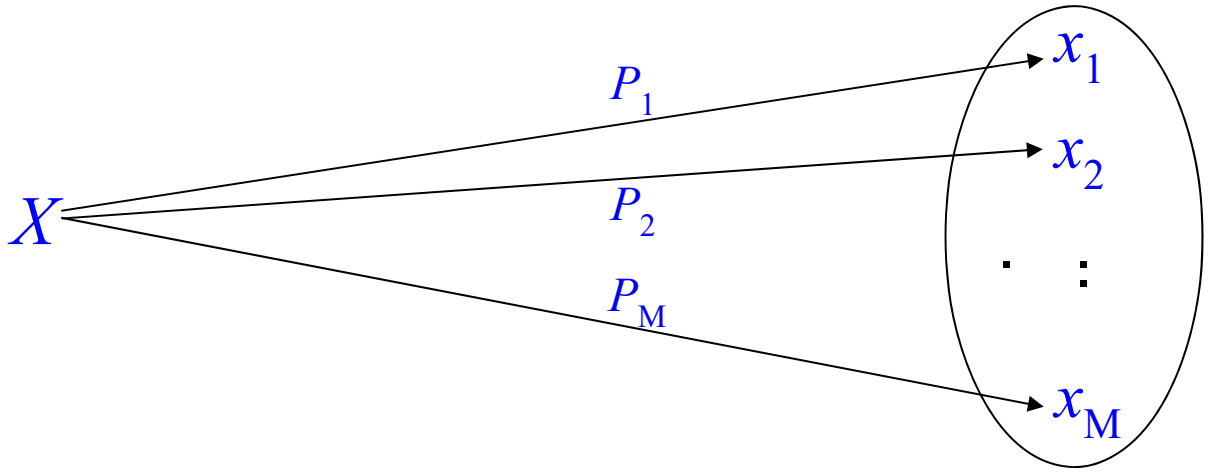
Task of stat. mech. is to find this probability distribution and then explain further the macroscopic quantities!

- Statistical Postulate (统计假说)
  - When an isolated system is left alone long enough time, it evolves to thermal equilibrium.
  - Equilibrium is not one microstate, but rather that probability distribution of microstates having the greatest possible disorder allowed by the physical constraints on the system.

Key question: How to measure disorder?

Measure disorder

Event Probability Possible values



- A good quantity (I) to measure disorder satisfies
  - Continuity: continuous respect to $P_1, P_2, \ldots, P_M$
  - Zero for pure state: $I=0$ for {P_1=1 and others=0} and Maximum for most mixed state: max I for {P_j=1/M}
  - Additivity: $I(X+Y)=I(X)+I(Y)$ for independent X and Y

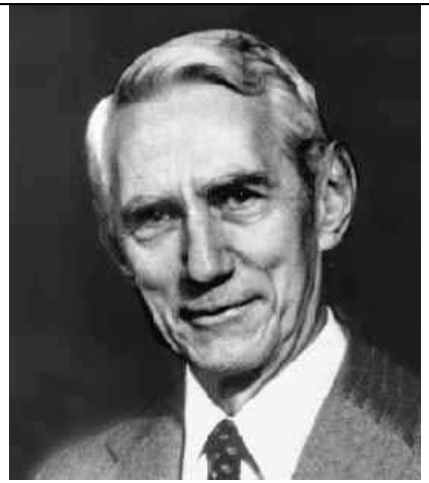
- Shannon's information entropy (1948)

$$I = -\sum_{j=1}^{M} P_j \ln P_j$$

Theorem 2: The only H satisfying the three above assumptions is of the form:

$$H = -K \sum_{i=1}^{n} p_i \log p_i$$

where K is a positive constant.



The Bell System Technical Journal

Vol. XXVII *July, 1948* *No. 3*

A Mathematical Theory of Communication

By C. E. SHANNON

Problem: prove that $I_{max} = \ln M$ if and only if $P_j = 1/M$.

(1) constraint: $\sum_{j=1}^{M} P_j = 1$

(2) Lagrange problem: （含有约束条件下的函数极值问题）

$$extremum\left\{\tilde{I} = -\sum_{j=1}^{M} P_j \ln P_j - \lambda\left(\sum_{j=1}^{M} P_j - 1\right)\right\}$$

Shannon熵　　归一化条件　　λ拉格朗日乘子

$$\partial \tilde{I} / \partial P_j = 0 \Rightarrow P_j = e^{-(1+\lambda)} \quad \text{(const.)}$$

$$\partial I / \partial = 0 \Rightarrow \sum_{j=1}^{M} P_j = 1 \longrightarrow P_j = 1/M$$

(3) Max. or Min. ?:

$$\left.\frac{\partial^2 \tilde{I}}{\partial P_j \partial P_k}\right|_{P_j = 1/M} = -M\delta_{jk} \Rightarrow \text{maximum!}$$

Boltzmann Entropy

- Equilibrium of isolated system: const. $E,\ N,\ V$

$W(E,N,V)$: the number of allowed microstates

Measure of disorder: $I = -\sum_{j=1}^{W} P_j \ln P_j$

Constraint: $\sum_{j=1}^{W} P_j = 1$

$\Rightarrow P_j = \frac{1}{W}$

Each microstate is equally probable! $I = I_{max}$

$$S \equiv k_B I_{max} = k_B \ln W$$ (Boltzmann entropy)

Boltzmann Entropy = constant X maximal value of disorder

- Canonical system: A system in equilibrium state at constant N, V & $\langle E \rangle$

Allowed microsates: $\Gamma_j = \{(r_1, p_1; r_2, p_2; \cdots; r_N, p_N)\}_j$

with energy $E_j; j = 1,2, \cdots$ Probability: $P_j = P(E_j)$

Measure of disorder: $I = -\sum_j P_j \ln P_j$

Constraints: $\sum_j P_j = 1$ $\sum_j P_j E_j = const.$

Problem: prove that $\max\{I\}$ with the above constraints gives

$$P_j = e^{-\beta E_j}/Z$$ ---Boltzmann distribution

where β is a constant and $Z = \sum_j e^{-\beta E_j}$ ---Partition function

Hint for Boltzmann distribution

New entropy function with two Lagrange multipliers:

$$\tilde{S} = -\sum_j P_j \ln P_j - \lambda\left(\sum_j P_j - 1\right) - \beta\left(\sum_j P_j E_j - \langle E \rangle\right)$$

Shannon熵　　归一化条件　　平均能量约束

then

$$\frac{\partial S}{\partial P_j} = \cdots = 0$$

T and *F* in Stat. Mech.

Problem: if we interpret $\langle E \rangle = U$, what's the physical meaning of β?

$$P_j = e^{-\beta E_j}/Z \Rightarrow U = \langle E \rangle = \sum_j E_j\, e^{-\beta E_j}/Z \qquad (Z = \sum_j e^{-\beta E_j})$$

$$S \equiv k_B I_{max} = -k_B \sum_j P_j \ln P_j = -k_B \sum_j P_j \ln\left(\frac{e^{-\beta E_j}}{Z}\right)$$

$$= -k_B \sum_j P_j \left(-\beta E_j - \ln Z\right) = k_B \beta U + k_B \ln Z$$

For constant N, V

$$\frac{\partial U}{\partial \beta} = U^2 - \langle E^2 \rangle$$

(Homework: proof 2 equations)

$$\frac{\partial S}{\partial \beta} = k_B \beta [U^2 - \langle E^2 \rangle]$$

$$\Rightarrow \frac{\partial S}{\partial U}\Big|_{N,V} = k_B \beta$$

Thermodynamic relation in isochoric (等容) reversal process $dU = TdS$

$$\Rightarrow \frac{\partial S}{\partial U}\Big|_{N,V} = \frac{1}{T}$$

$$\boxed{\beta = \frac{1}{k_B T}}$$

- Temperature in Stat. Mech.

S and U for constant V and N can be calculated in Stat. Mech.

We can define

$$\frac{1}{T} = \left.\frac{\partial S}{\partial U}\right|_{N,V}$$

Then Stat. Mech. & thermodynamics are consistent.

- Free energy in Stat. Mech.

$$P_j = e^{-\beta E_j}/Z \qquad Z = \sum_j e^{-\beta E_j} \qquad \beta = 1/k_B T$$

$$U = \langle E \rangle = \sum_j E_j \, e^{-\beta E_j}/Z$$

$$S = k_B I_{\max} = k_B \beta U + k_B \ln Z$$

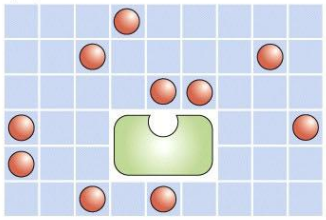
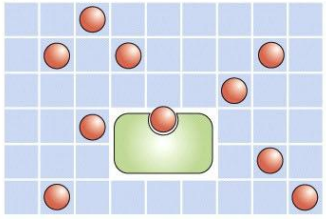
Problem: prove that $\boxed{F = -\, k_B T \ln Z}$

Problem: prove that $\boxed{U = -\,\dfrac{\partial \ln Z}{\partial \beta}}$

§ 4.2 Simple applications: ligand-receptor binding & gene expression

Ligand-receptor binding

- Lattice model

STATE	ENERGY	MULTIPLICITY	WEIGHT
(A) 	$L\varepsilon_{sol}$	$\frac{\Omega!}{L!(\Omega-L)!} \approx \frac{\Omega^L}{L!}$	$\frac{\Omega^L}{L!} e^{-\beta L\varepsilon_{sol}}$
(B) 	$(L-1)\varepsilon_{sol} + \varepsilon_b$	$\frac{\Omega!}{(L-1)!(\Omega-L+1)!} \approx \frac{\Omega^{L-1}}{(L-1)!}$	$\frac{\Omega^{L-1}}{(L-1)!} e^{-\beta[(L-1)\varepsilon_{sol} + \varepsilon_b]}$

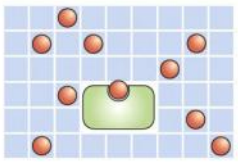
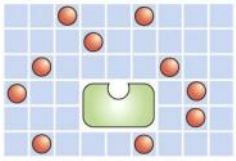
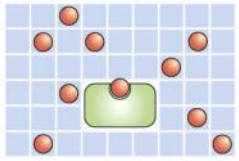
Number of ligand

Number of lattice

For $L \ll \Omega$

$$\frac{\Omega!}{(\Omega - L)!} \approx \Omega^L$$

Binding probability

$$p_{bound} = \frac{\sum_{states} \left(\text{  } \right)}{\sum_{states} \left(\text{  } \right) + \sum_{states} \left(\text{  } \right)} = \frac{\frac{\Omega^{L-1}}{(L-1)!} e^{-\beta[(L-1)\varepsilon_{sol} + \varepsilon_b]}}{\frac{\Omega^{L-1}}{(L-1)!} e^{-\beta[(L-1)\varepsilon_{sol} + \varepsilon_b]} + \frac{\Omega^L}{L!} e^{-\beta L\varepsilon_{sol}}}$$

- Binding curve

$$p_{bound} = \frac{(L/\Omega)\mathrm{e}^{-\beta\Delta\varepsilon}}{1+(L/\Omega)\mathrm{e}^{-\beta\Delta\varepsilon}} \qquad \Delta\varepsilon = \varepsilon_b - \varepsilon_{sol}$$

$$\xrightarrow[C_0 = \Omega/V_{tot}]{C = L/V_{tot}} \quad p_{bound} = \frac{(c/c_0)\mathrm{e}^{-\beta\Delta\varepsilon}}{1+(c/c_0)\mathrm{e}^{-\beta\Delta\varepsilon}}$$

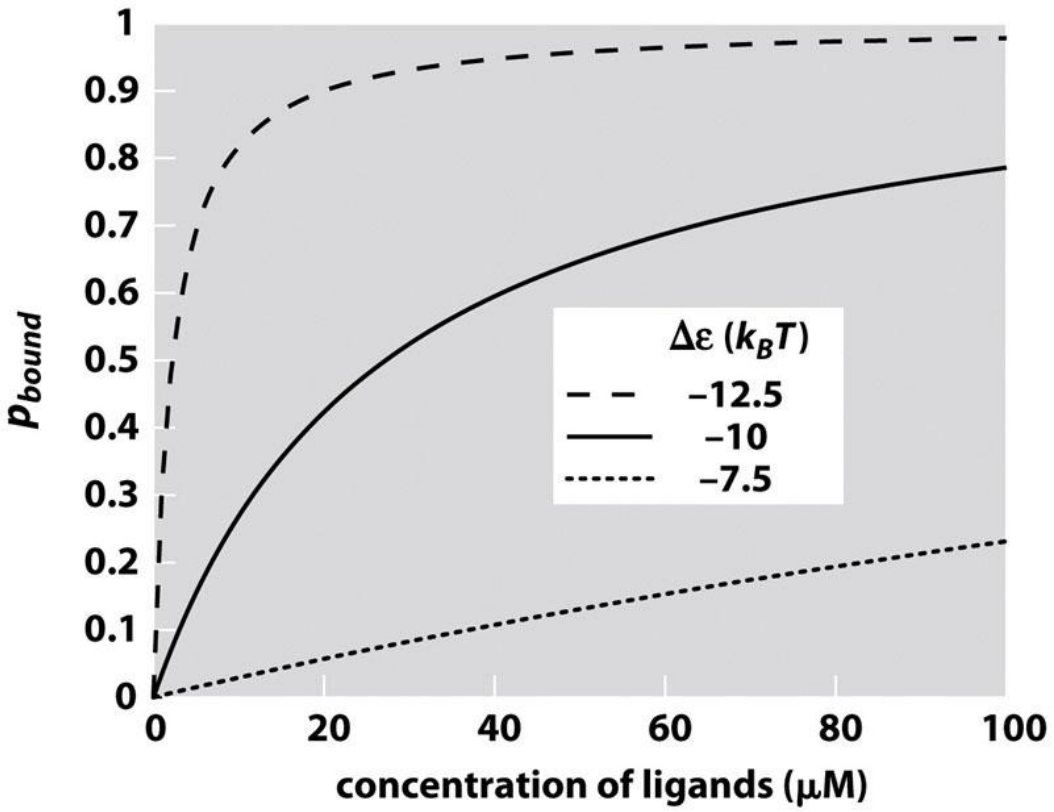
Hill function with Hill coefficient n=1

Assume lattice constant ~1nm

$$\rightarrow c_0 = \frac{1}{(1\,\mathrm{nm})^3} \approx 0.6\,\mathrm{M} \quad ? \rightarrow$$

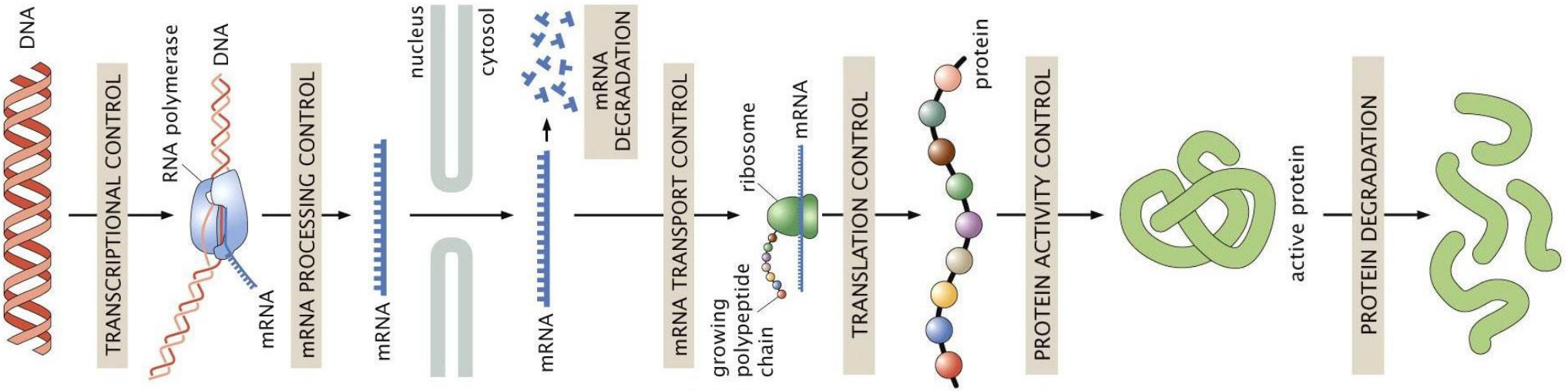
Question: which effect (energy or entropy) dominates at small c?

Answer: entropy



Gene expression

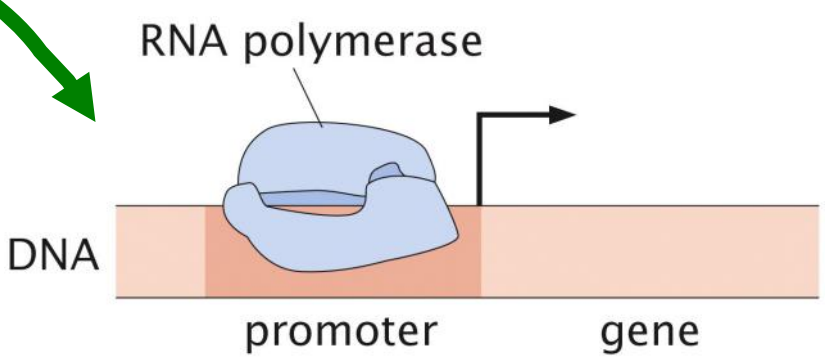
- Genetic control in the central dogma



simplify

Very complicated controls, simplified as a problem as

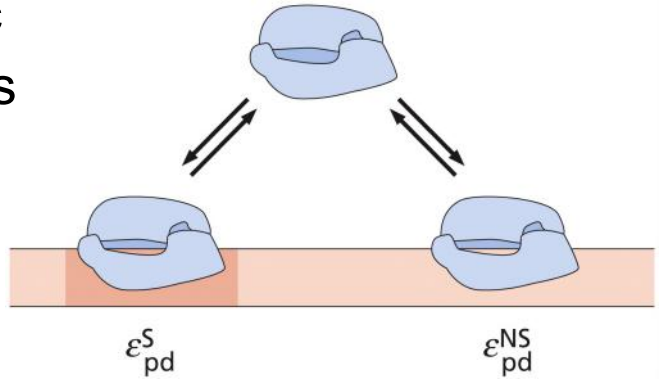
RNA polymerase binds at the promoter of the related gene

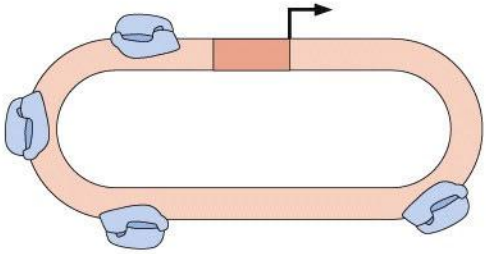
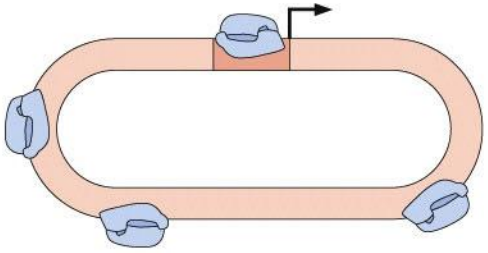


- # Lattice model

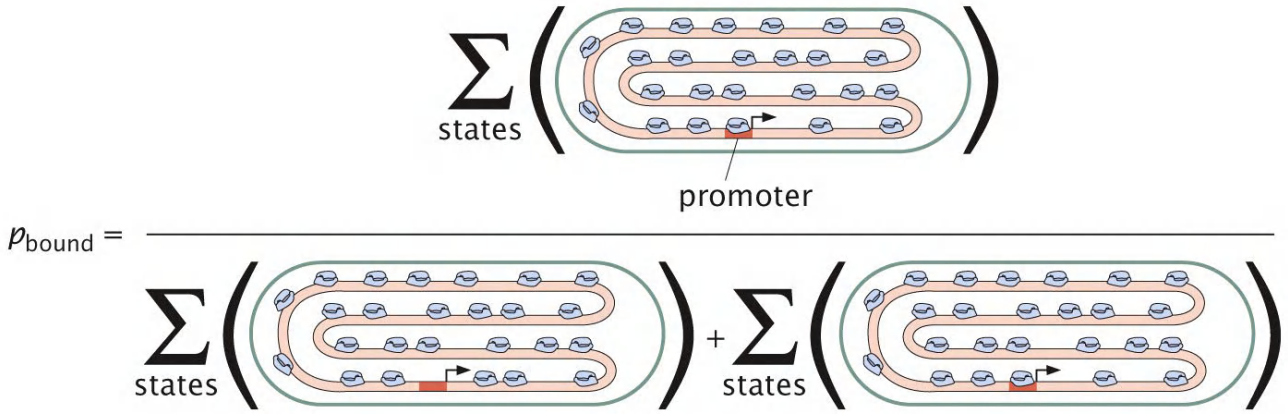
Experiment reveals most cellular RNA polymerase molecules are bound to DNA

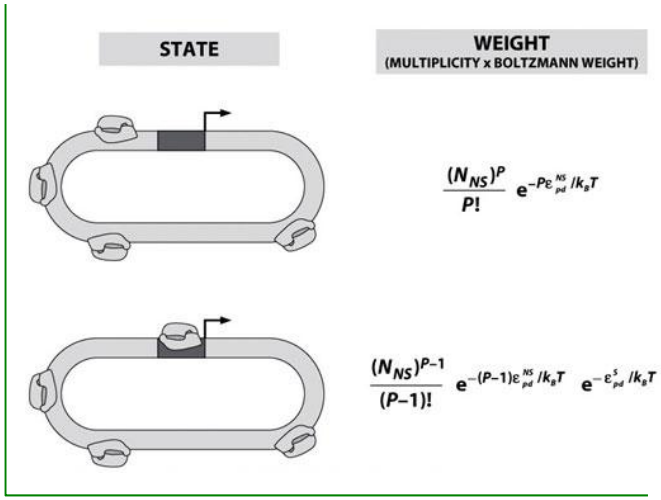
Assumption: (1) all RNA polymerase molecules are bound to DNA
(2) different binding energies for specific site (promoter) and non-specific sites
(3) P RNA polymerases and N_{NS} non-specific sites



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

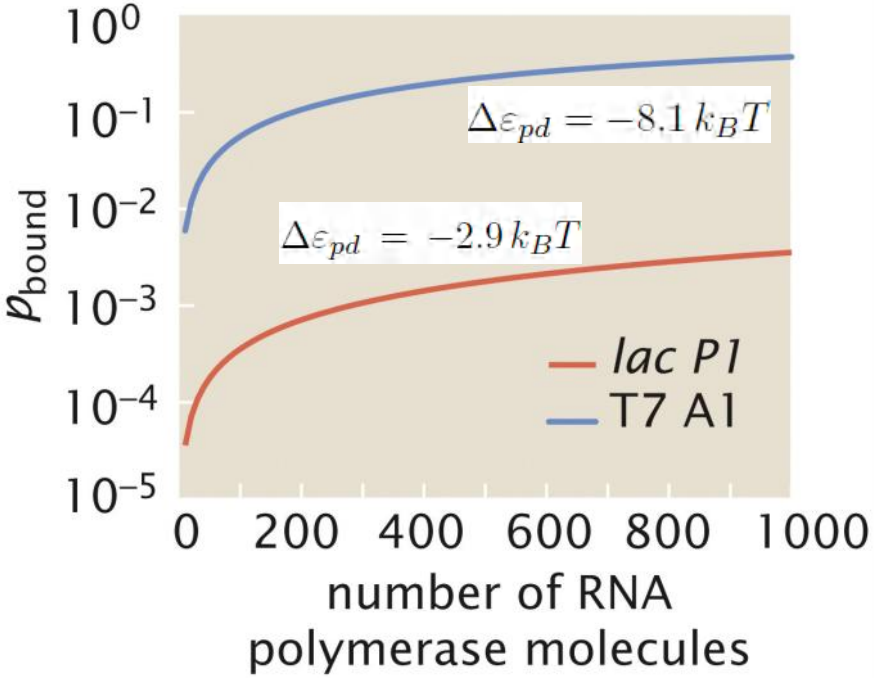
- Binding probability of RNA polymerase to its promoter





$$= \frac{\frac{N_{NS}^{P-1}}{(P-1)!} e^{-(P-1)\varepsilon_{pd}^{NS}/k_BT} e^{-\varepsilon_{pd}^{S}/k_BT}}{\frac{N_{NS}^{P}}{P!} e^{-\varepsilon_{pd}^{S}/k_BT} + \frac{N_{NS}^{P-1}}{(P-1)!} e^{-(P-1)\varepsilon_{pd}^{NS}/k_BT} e^{-\varepsilon_{pd}^{S}/k_BT}}$$

$$= \frac{\frac{P}{N_{NS}} e^{-\beta\Delta\varepsilon_{pd}}}{1 + \frac{P}{N_{NS}} e^{-\beta\Delta\varepsilon_{pd}}} = \frac{1}{1 + \frac{N_{NS}}{P} e^{\beta\Delta\varepsilon_{pd}}}$$



with $\Delta\varepsilon_{pd} = \varepsilon_{pd}^{S} - \varepsilon_{pd}^{NS}$ ⟶ Determine the shapes of bind curve

§ 4.3 Two-state model

Internal state variable

- Examples of the internal state variable description of macromolecules

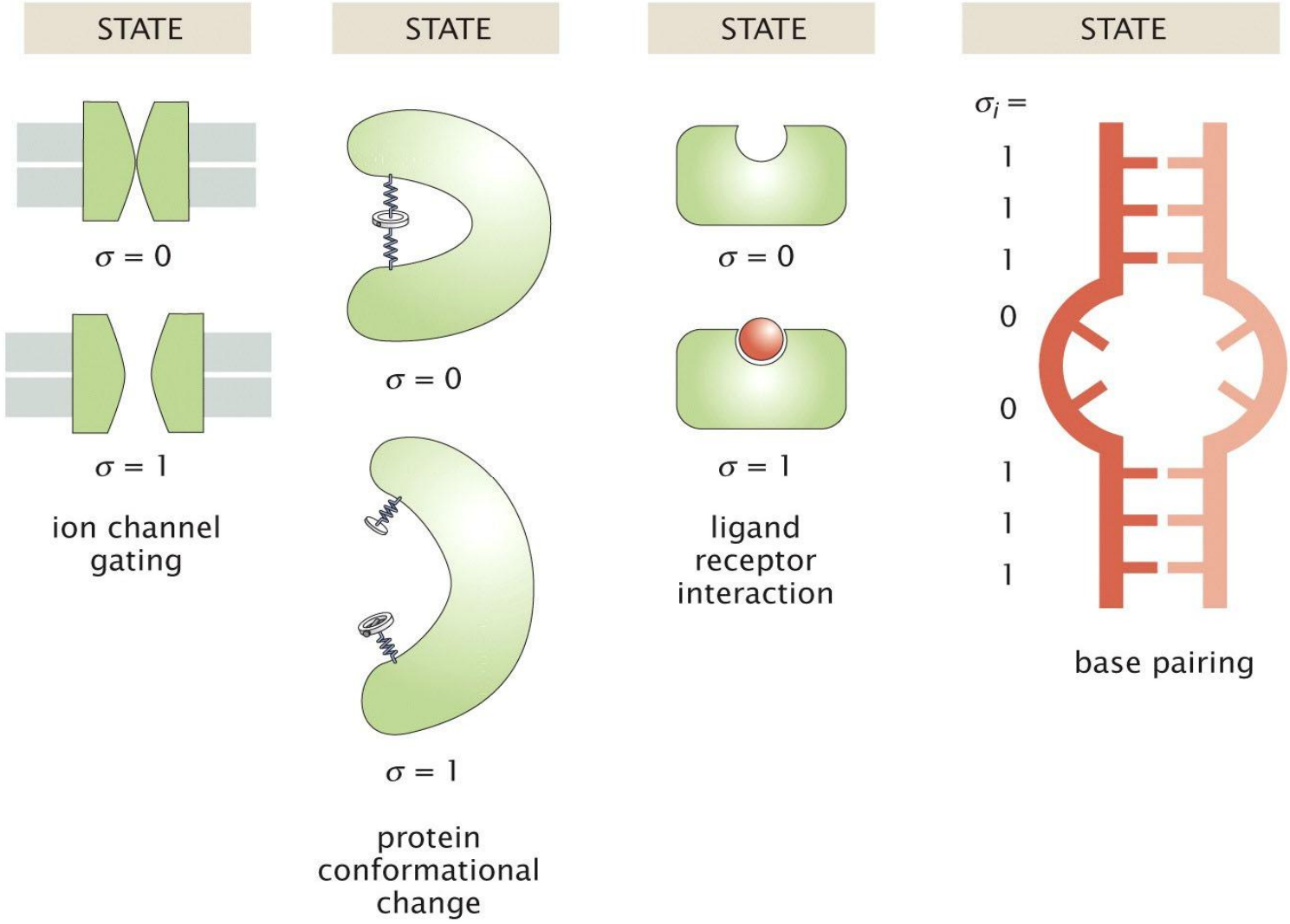


Figure 7.1 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

- Current trajectories and open probability for Na^+ channel subjected to different voltages

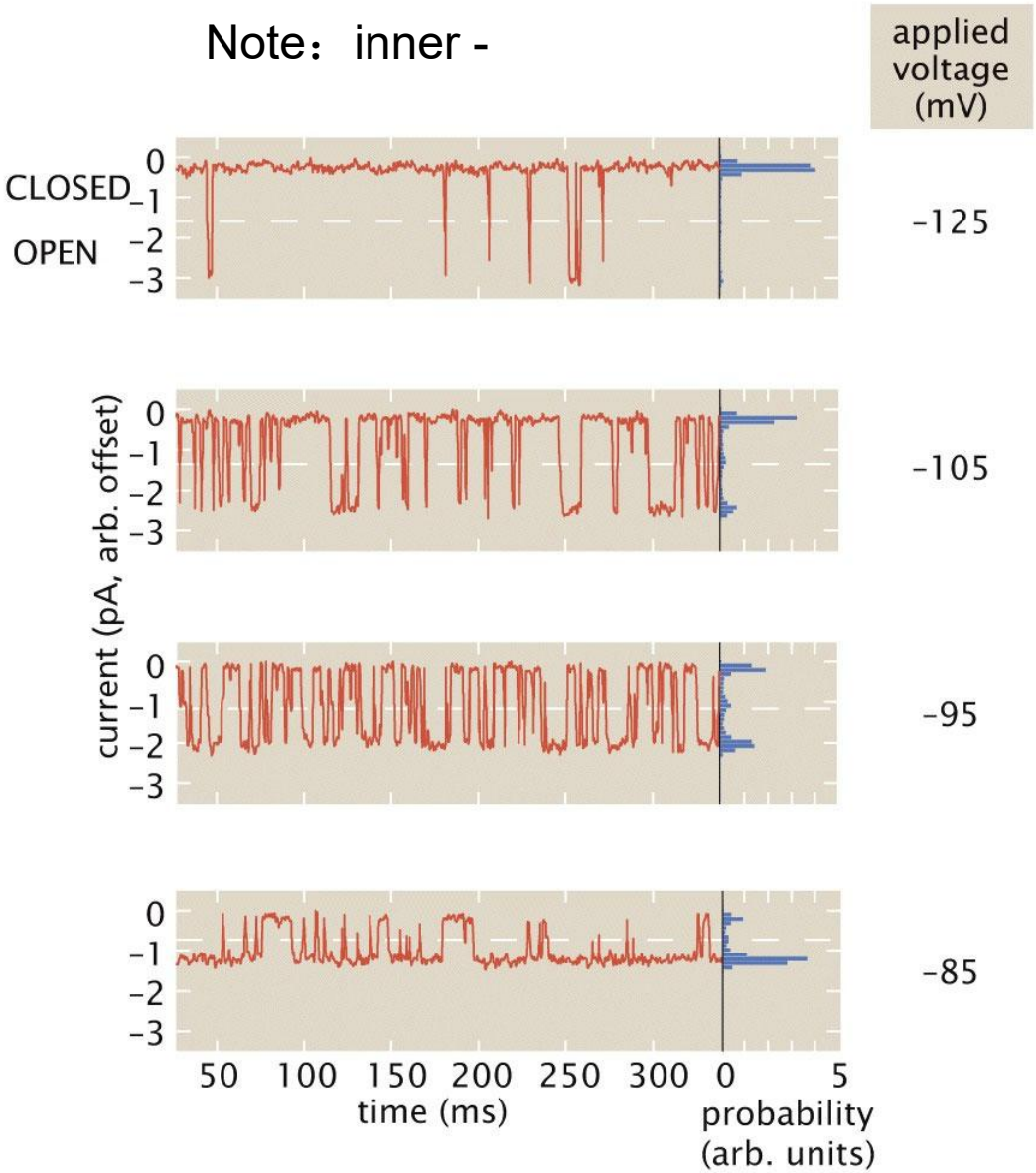


Figure 7.2b Physical Biology of the Cell, 2ed. (© Garland Science 2013)

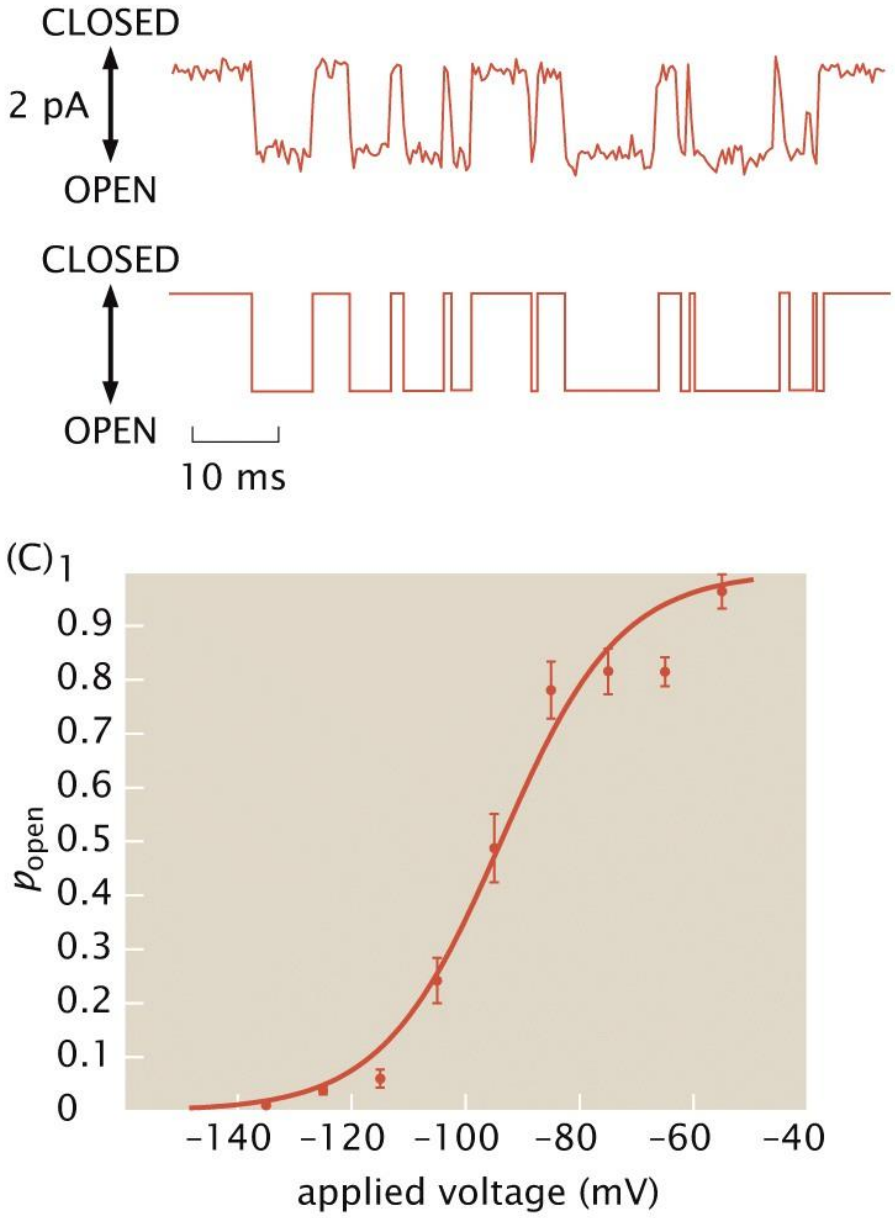


Figure 7.2a Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Ion channel

- Energy landscape

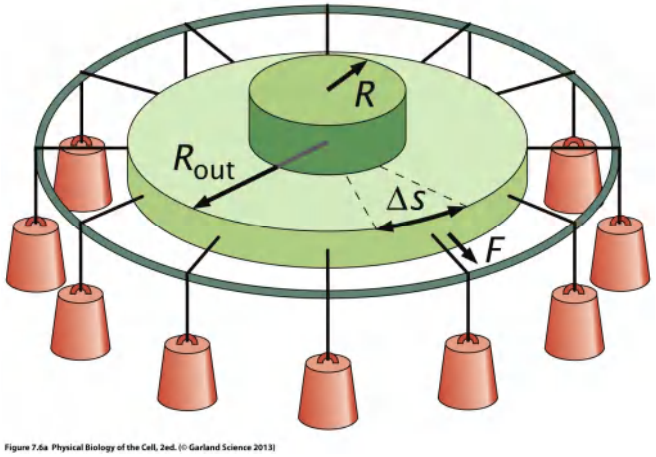


Figure 7.6a Physical Biology of the Cell, 2ed. (© Garland Science 2013)

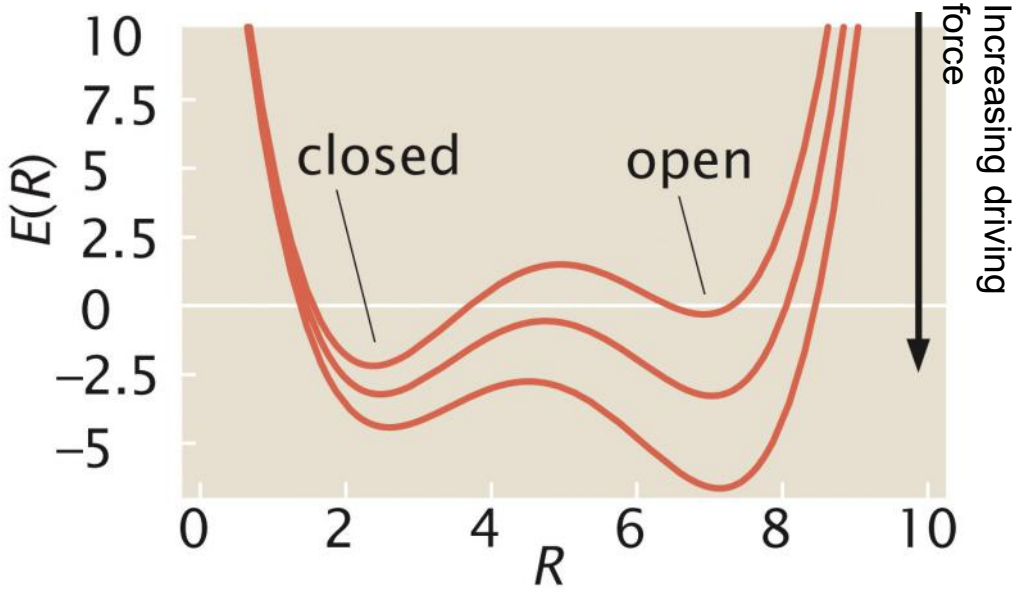
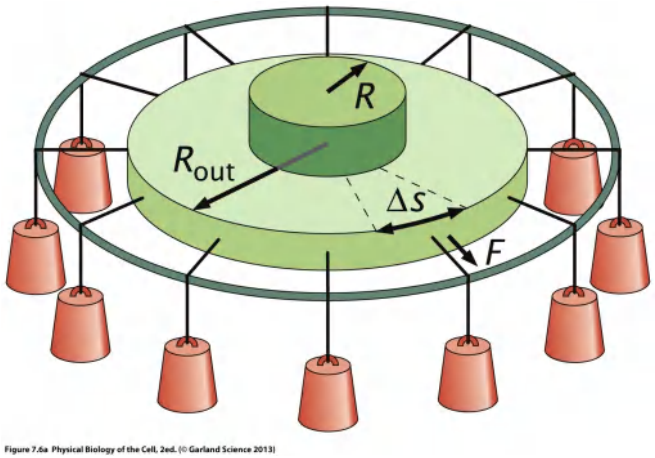
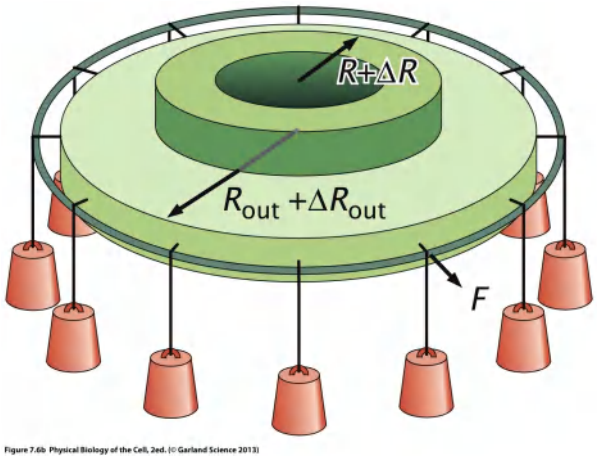


Figure 7.7 Physical Biology of the Cell, 2ed. (© Garland Science 2013)





Incompressiblity of membrane ⇨ $2\pi R\Delta R = 2\pi R_{out}\Delta R_{out}$ ⇨ $\Delta R_{out} = \frac{R}{R_{out}}\Delta R$

$$F = \tau \Delta s \Rightarrow \Delta G_{tension} = \underbrace{\tau \Delta s}_{\text{force on arc}} \times \underbrace{\frac{R}{R_{out}}\Delta R}_{\text{displacement of patch}} \times \underbrace{\frac{2\pi R_{out}}{\Delta s}}_{\text{no. of "patches"}}$$

$$= -\tau 2\pi R\Delta R = -\tau \Delta A \Rightarrow$$

$$E(\sigma) = \sigma\epsilon_{open} + (1-\sigma)\epsilon_{closed} - \sigma\tau\Delta A$$

σ= 0, closed; 1, open

- Open probability

$$E(\sigma) = \sigma\epsilon_{open} + (1-\sigma)\epsilon_{closed} - \sigma\tau\Delta A$$

$$Z = \sum_{\sigma=0}^{1} e^{-\beta E(\sigma)} = e^{-\beta\epsilon_{closed}} + e^{-\beta(\epsilon_{open} - \tau\Delta A)}$$

$$p_{open} = \frac{e^{-\beta(\epsilon_{open} - \tau\Delta A)}}{e^{-\beta(\epsilon_{open} - \tau\Delta A)} + e^{-\beta\epsilon_{closed}}}$$

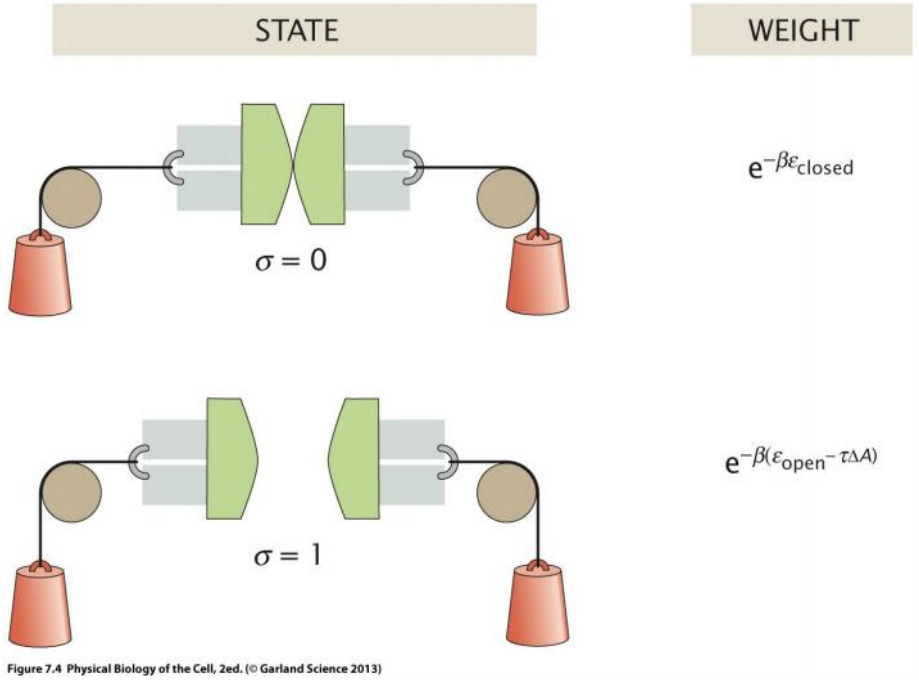


Figure 7.4 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

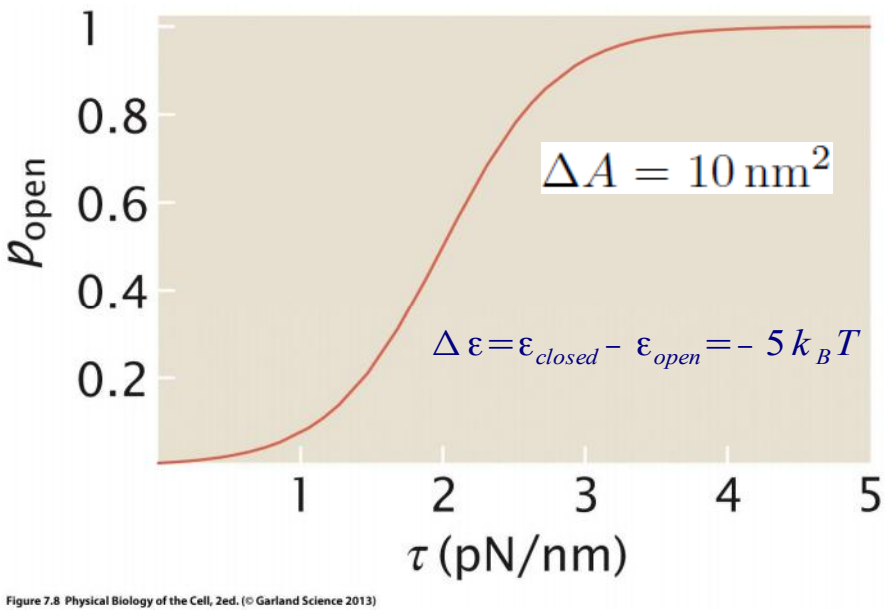


Figure 7.8 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

[Nat. Struc. Biol. 9: 696 (2002)]

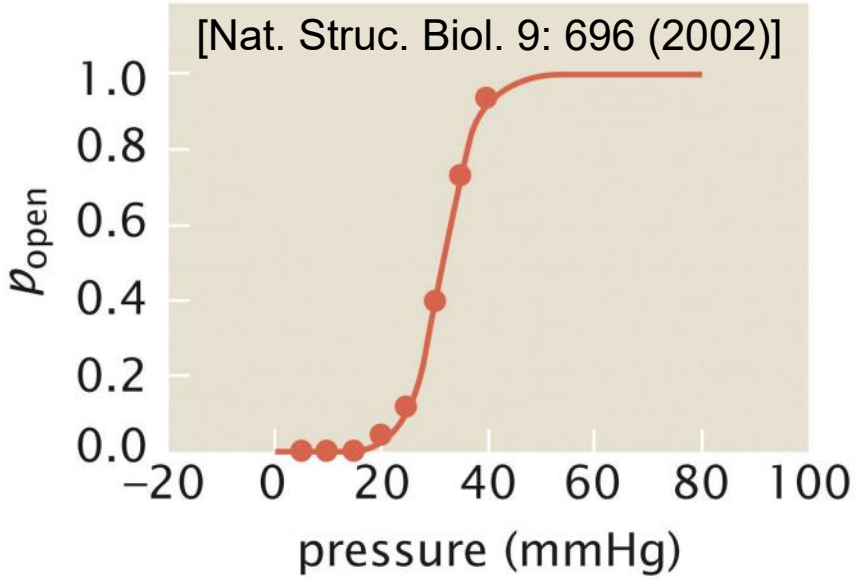


Figure 7.5 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Phosphorylation (磷酸化)

- Phosphorylation can alter the relative energies of the active and inactive states of enzymes

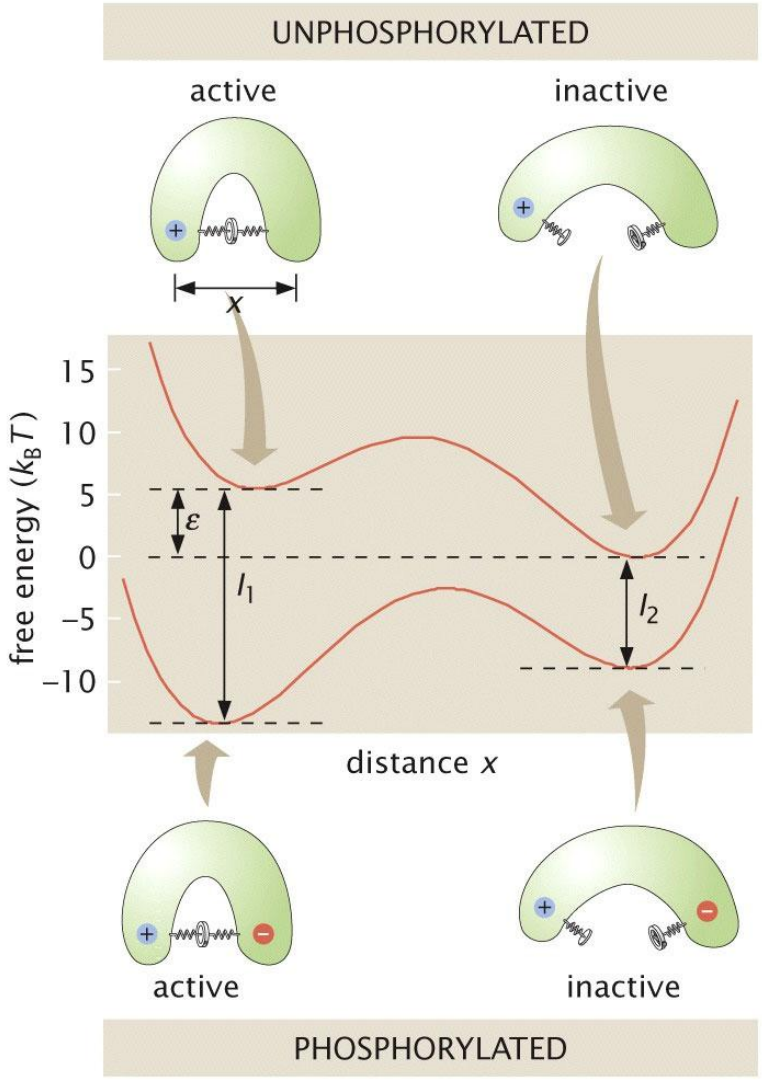


Figure 7.12 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

The addition of a phosphate group introduces a favorable electrostatic interaction which lowers the active state free energy with respect to the inactive state free energy

$\sigma_S = 0$ inactive state
$\sigma_S = 1$ active state

$\sigma_P = 0$ unphosphorylated state
$\sigma_P = 1$ phosphorylated state

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

$$G(\sigma_P, \sigma_S) = \varepsilon\sigma_S - I_2\sigma_P + (I_2 - I_1)\sigma_S\sigma_P$$

Probability in active states

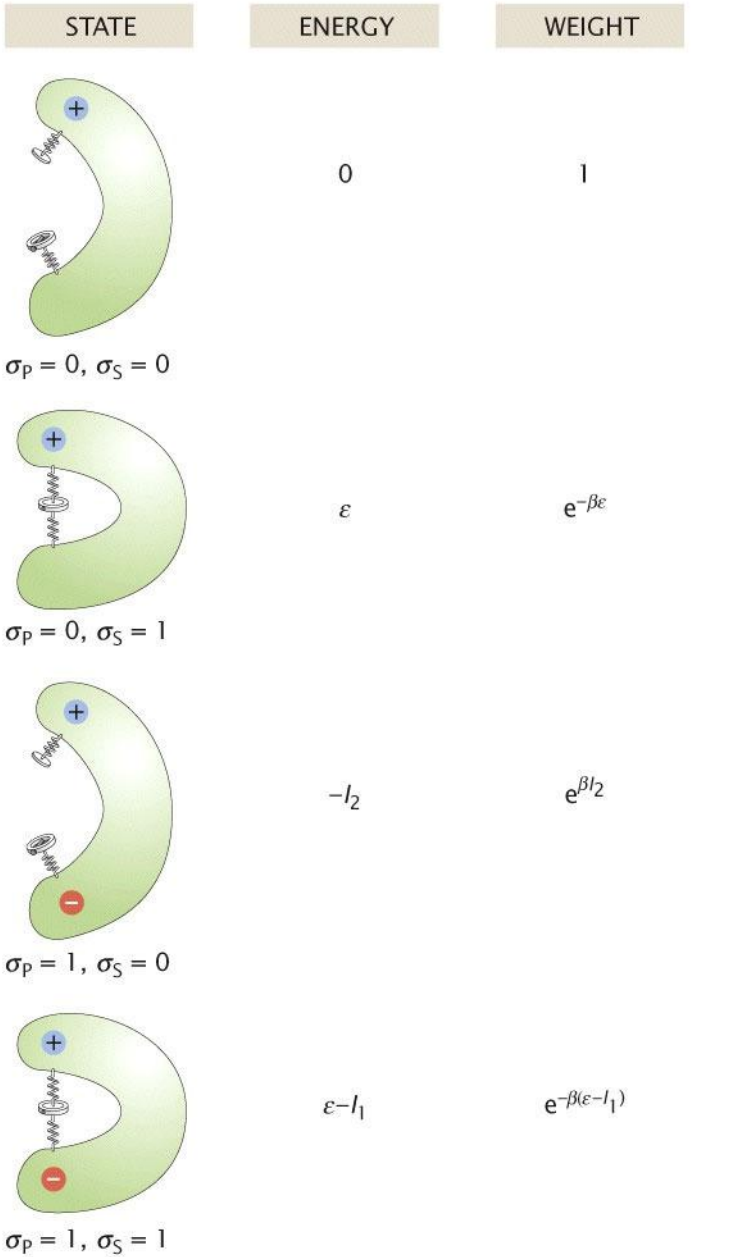


Figure 7.13 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Probability of the enzyme in active state, but not phosphorylated.

$$p_{active} = \frac{e^{-\beta G(\sigma_S=1,\sigma_P=0)}}{\sum_{\sigma_S=0,1} e^{-\beta G(\sigma_S,\sigma_P=0)}} = \frac{e^{-\beta\varepsilon}}{e^{-\beta\varepsilon}+1}$$

Probability of the enzyme in active state when phosphorylated.

$$p^*_{active} = \frac{e^{-\beta G(\sigma_S=1,\sigma_P=1)}}{\sum_{\sigma_S=0,1} e^{-\beta G(\sigma_S,\sigma_P=1)}} = \frac{e^{-\beta(\varepsilon-I_1)}}{e^{-\beta(\varepsilon-I_1)}+e^{\beta I_2}}$$

$$\frac{p^*_{active}}{p_{active}} = \frac{1+e^{\beta\varepsilon}}{1+e^{\beta(\varepsilon+I_2-I_1)}} \approx 150$$

when $\varepsilon \approx 5\,k_BT$ $\quad I_2 - I_1 \approx -10\,k_BT$

天然蛋白质的失活态具有更低自由能，所以更多分子处于失活状态。
磷酸化让分子活性态的自由能更低，让分子处于活性态。

Gibbs distribution

- Open system with particle and energy exchanges

$$N_s + N_r = N_u \quad \text{=const.}$$

$$E_s + E_r = E_u \quad \text{=const.}$$

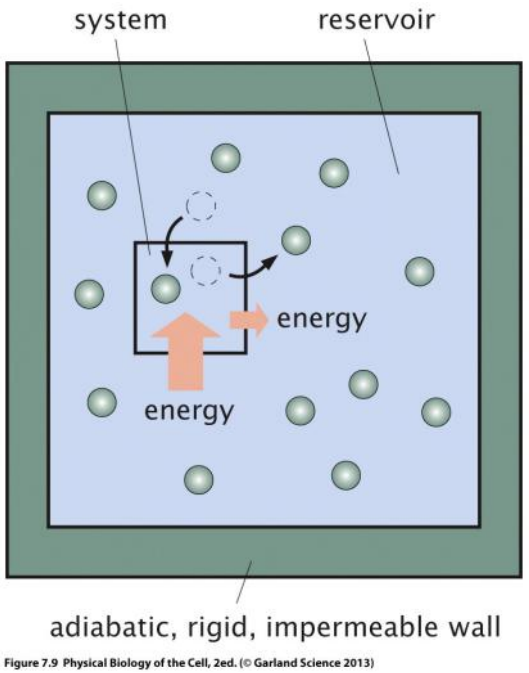


Figure 7.9 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

When the system stays a given state $(E_s^{(i)}, N_s^{(i)})$, the number of states that the universe (=system+reservoir)

$$W_u(E_s^{(i)}, N_s^{(i)}) = \underbrace{1}_{\text{states of system}} \times \underbrace{W_r(E_u - E_s^{(i)}, N_u - N_s^{(i)})}_{\text{states of reservoir}}$$

Probability of finding a given state of the system

$$p(E_s^{(i)}, N_s^{(i)}) = \frac{W_u(E_s^{(i)}, N_s^{(i)})}{\sum_i W_u(E_s^{(i)}, N_s^{(i)})} \propto W_r(E_u - E_s^{(i)}, N_u - N_s^{(i)})$$

Given $E_s^{(i)}$ and $N_s^{(i)}$, we have $S_r(E_u - E_s^{(i)}, N_u - N_s^{(i)}) = k_B \ln W_r(E_u - E_s^{(i)}, N_u - N_s^{(i)})$

- Gibbs distribution & grand partition function

$$p\left(E_s^{(i)}, N_s^{(i)}\right) \propto \mathrm{e}^{S_r(E_u - E_s^{(i)}, N_u - N_s^{(i)})/k_B}$$

$$S_r(E_u - E_s^{(i)}, N_u - N_s^{(i)}) = S_r(E_u, N_u) - \frac{\partial S_r}{\partial E_r} E_s^{(i)} - \frac{\partial S_r}{\partial N_r} N_s^{(i)}$$

$$(\partial S/\partial E)_{V,N} = 1/T \qquad (\partial S/\partial N)_{E,V} = -\mu/T$$

$$p\left(E_s^{(i)}, N_s^{(i)}\right) \propto \mathrm{e}^{-\beta(E_s^{(i)} - \mu N_s^{(i)})} = \frac{\mathrm{e}^{-\beta(E_s^{(i)} - \mu N_s^{(i)})}}{Z}$$

μ化学势

$$\mathcal{Z} = \sum_i e^{-\beta(E_s^{(i)} - N_s^{(i)}\mu)}$$

Z是巨配分函数，所有可能微观态i的求和

$$\langle N \rangle = \frac{1}{\mathcal{Z}} \sum_i N_i e^{-\beta(E_i - N_i\mu)} = \frac{1}{\beta} \frac{\partial}{\partial \mu} \ln \mathcal{Z}$$

巨配分函数直接计算系统的平均粒子数

回顾：配分函数可以直接计算自由能和平均能量

$$F = -k_B T \ln Z \qquad \langle E \rangle = -\frac{\partial}{\partial \beta} \ln Z$$

Simple ligand-receptor binding revisited with Gibbs distribution

- two states
  - Empty state $\sigma = 0$
  - Occupied state $\sigma = 1$

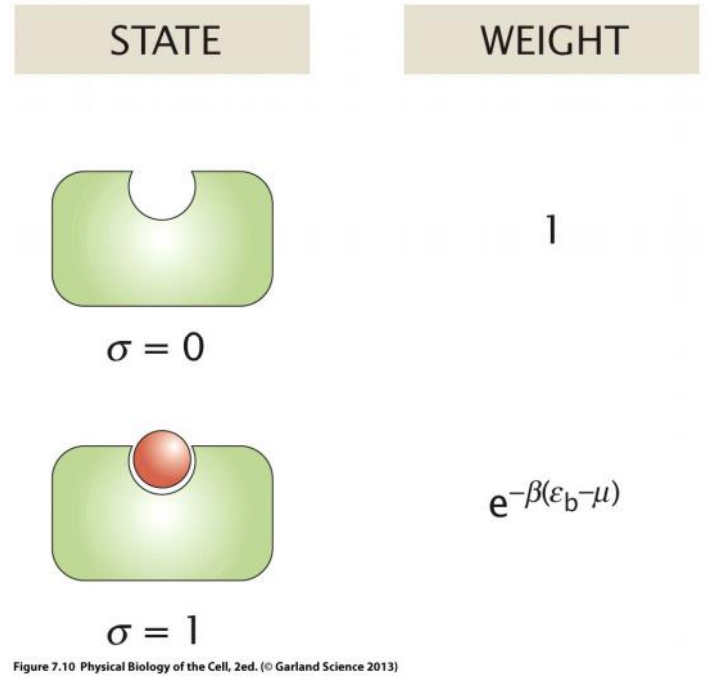


Figure 7.10 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

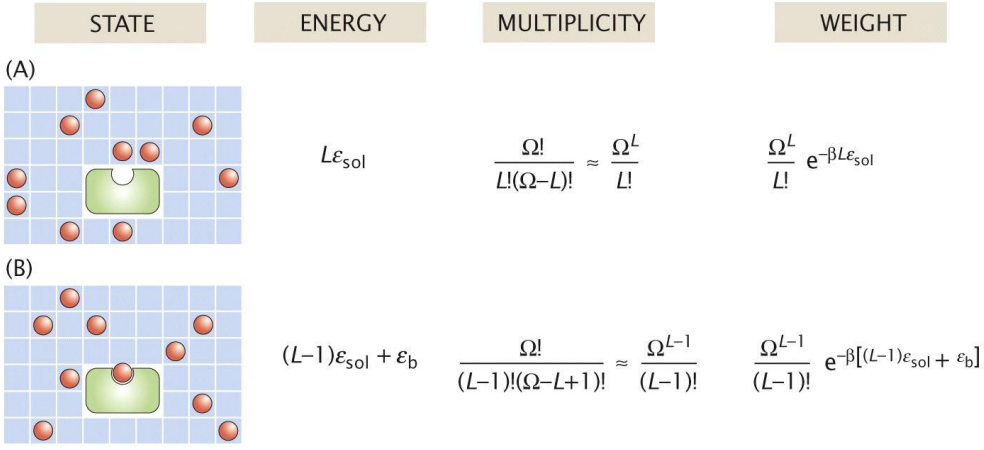
$$\mathcal{Z} = \sum_{\sigma=0}^{1} e^{-\beta(\varepsilon_b \sigma - \mu\sigma)}$$

$$= 1 + e^{-\beta(\varepsilon_b - \mu)}$$

$$\begin{cases} \langle N \rangle = 0 \times p_0 + 1 \times p_1 = p_1 = \dfrac{e^{-\beta(\varepsilon_b - \mu)}}{1 + e^{-\beta(\varepsilon_b - \mu)}} \\ \langle N \rangle = \dfrac{1}{\beta}\dfrac{\partial}{\partial \mu} \ln \mathcal{Z} = \dfrac{e^{-\beta(\varepsilon_b - \mu)}}{1 + e^{-\beta(\varepsilon_b - \mu)}} \\ \mu = \mu_0 + k_B T \ln(c/c_0) \end{cases}$$

$$\begin{cases} \langle N \rangle = \dfrac{(c/c_0)e^{-\beta\Delta\varepsilon}}{1 + (c/c_0)e^{-\beta\Delta\varepsilon}} \\ \Delta\varepsilon = \varepsilon_b - \mu_0 \end{cases}$$

对比下图中玻尔兹曼分布的处理方式：
吉布斯分布仅关注受体上，不用考虑粒子库中的大量粒子



§ 4.4 Cooperative binding of Hemoglobin

Toy Model of a Dimeric Hemoglobin

- Ising like model

Cooperativity parameter

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

STATE	WEIGHT
	1
	$e^{-\beta(\varepsilon-\mu)}$
	$e^{-\beta(\varepsilon-\mu)}$
	$e^{-\beta(2\varepsilon+J-2\mu)}$

$$\mathcal{Z} = \underbrace{1}_{\text{unoccupied}} + \underbrace{e^{-\beta(\varepsilon-\mu)} + e^{-\beta(\varepsilon-\mu)}}_{\text{single occupancy}} + \underbrace{e^{-\beta(2\varepsilon+J-2\mu)}}_{\text{both sites occupied}}$$

$$p_0 = \frac{1}{Z}$$

$$p_1 = \frac{2\,e^{-\beta(\varepsilon-\mu)}}{Z}$$

$$p_2 = \frac{e^{-\beta(2\varepsilon+J-2\mu)}}{Z}$$

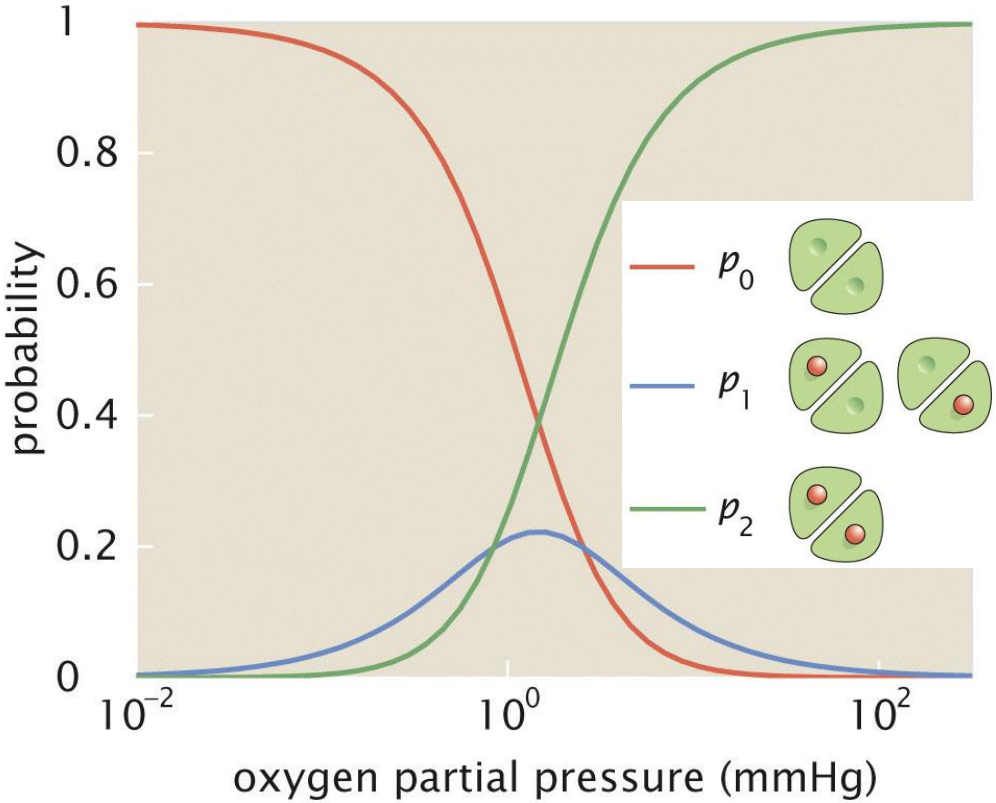
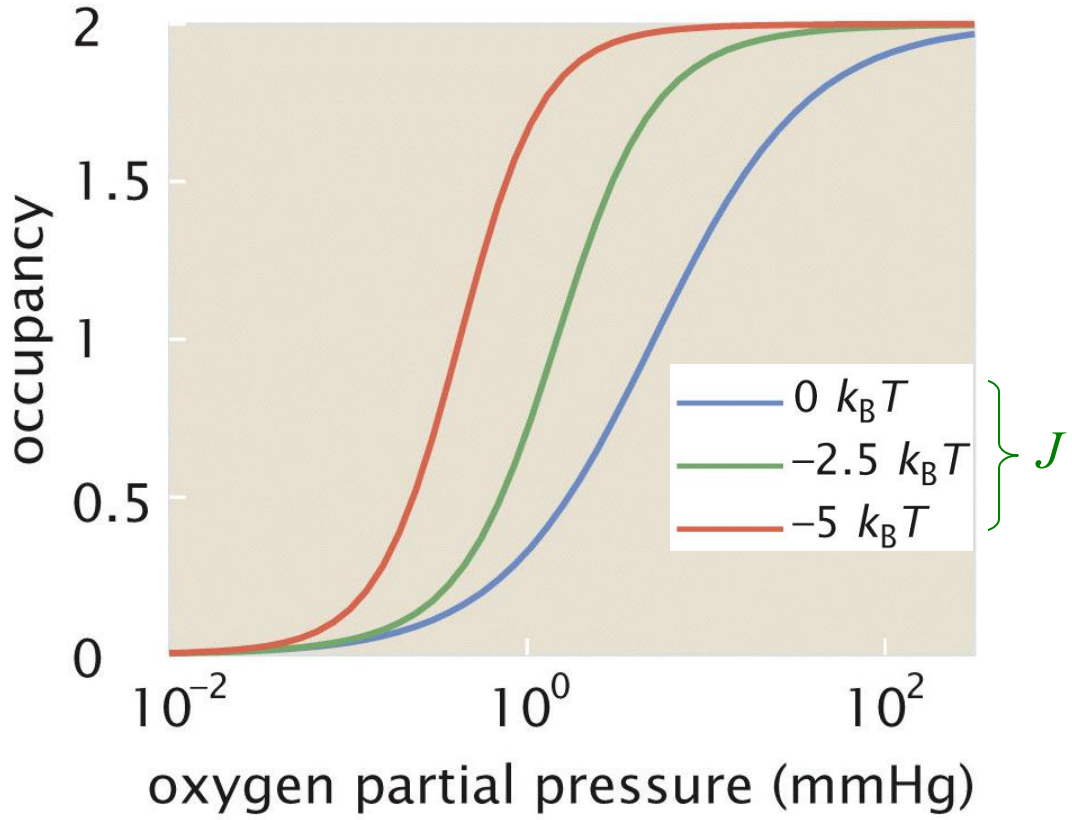


Figure 7.17 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

$$\langle N\rangle = 0\times p_0 + 1\times p_1 + 2\times p_2 = \frac{2\mathrm{e}^{-\beta(\varepsilon-\mu)} + 2\mathrm{e}^{-\beta(2\varepsilon+J-2\mu)}}{1+\mathrm{e}^{-\beta(\varepsilon-\mu)}+\mathrm{e}^{-\beta(\varepsilon-\mu)}+\mathrm{e}^{-\beta(2\varepsilon+J-2\mu)}}$$

$$\mu = \mu_0 + k_B T \ln(c/c_0)$$

$$\langle N_{bound}\rangle = \frac{2(c/c_0)\mathrm{e}^{-\beta\Delta\varepsilon} + 2(c/c_0)^2\mathrm{e}^{-\beta(2\Delta\varepsilon+J)}}{1+2(c/c_0)\mathrm{e}^{-\beta\Delta\varepsilon}+(c/c_0)^2\mathrm{e}^{-\beta(2\Delta\varepsilon+J)}}$$



$$\Delta\varepsilon = \varepsilon_b - \mu_0 = -5\,k_B T$$

$$c_0 = 760\,\mathrm{mmHg}$$

J=0, non-cooperativity

$$\langle N\rangle = 2\frac{(c/c_0)\mathrm{e}^{-\beta(\varepsilon_b-\mu_0)}}{1+(c/c_0)\mathrm{e}^{-\beta(\varepsilon_b-\mu_0)}}$$

Homework

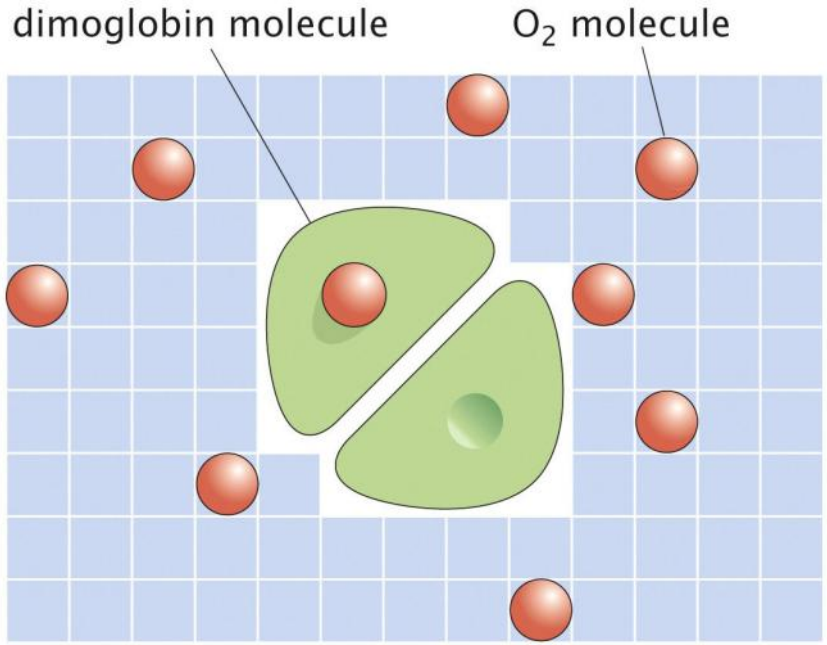


Figure 7.29 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

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

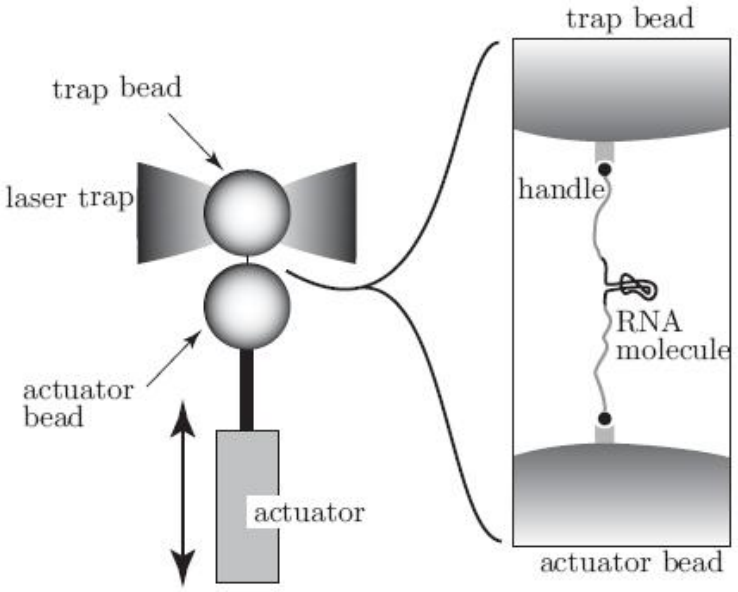
Use the canonical distribution to redo the problem of dimoglobin binding. For simplicity, imagine a box with N oxygen molecules which can be distributed amongst Ω sites.

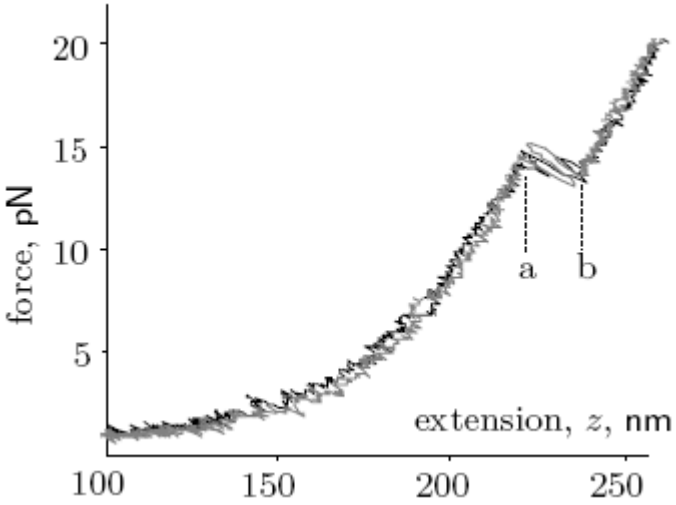
Calculate the probabilities p_0, p_1, and p_2 corresponding to occupancy 0, 1, and 2, Respectively. Draw the binding curves (i.e., the relations between p_0, p_1, p_2 and concentration of oxygen).

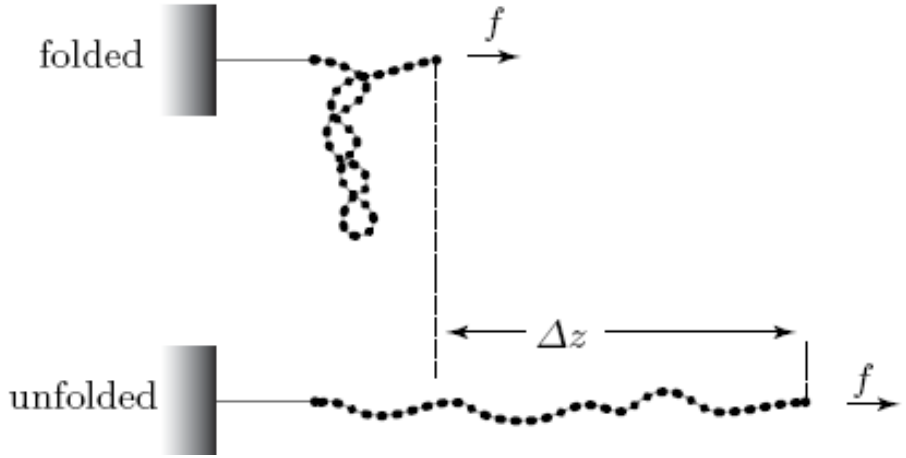
§ 4.5 RNA folding and unfolding

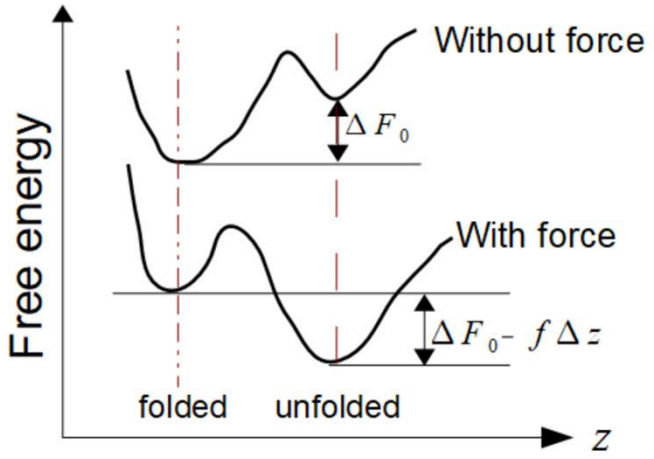
RNA folding as a two-state system

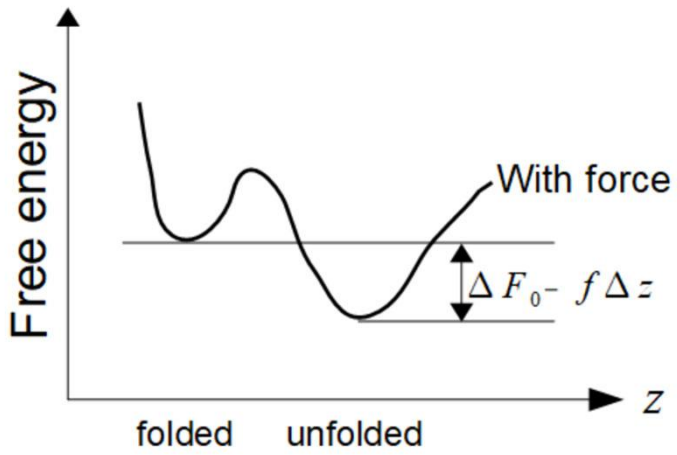
- Probability of folding and unfolding state





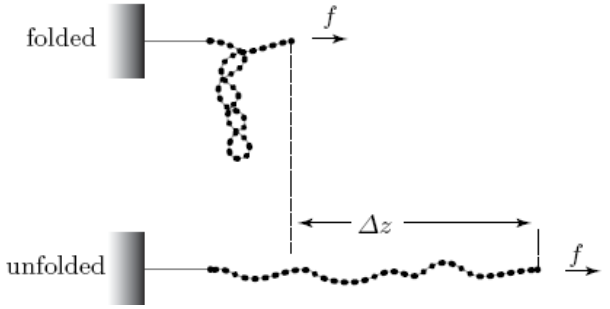






states

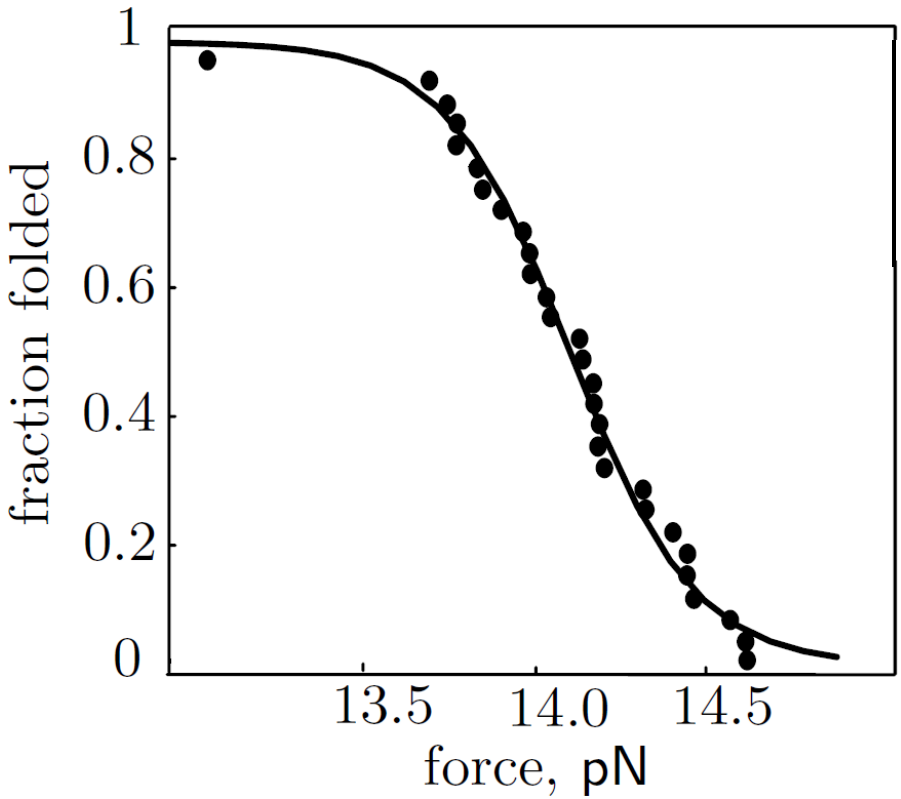
weights



1

$e^{-\beta(\Delta F_0 - f\Delta z)}$

$$\Rightarrow p_{fold} = \frac{1}{1+e^{-\beta(\Delta F_0 - f\Delta z)}}$$



Fit: $\Delta F_0 = 79 k_B T$, $\Delta z = 22$nm
Observed: $\Delta z \approx 22$nm

RNA folding and unfolding can be described indeed by the two-state model!

[Science **292** (2001) 733]

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Direct Measurement of Sequential Folding Pathway and Energy Landscape of Human Telomeric G-quadruplex Structures

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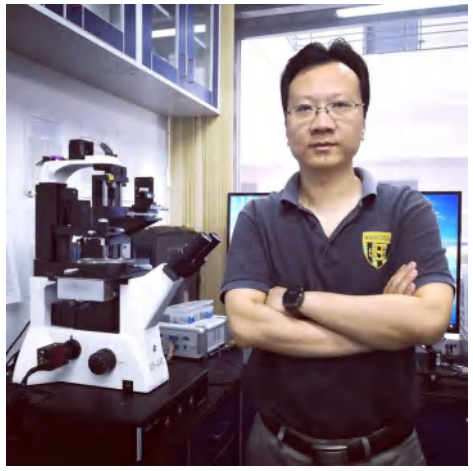
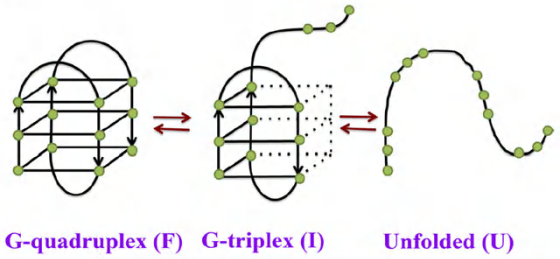
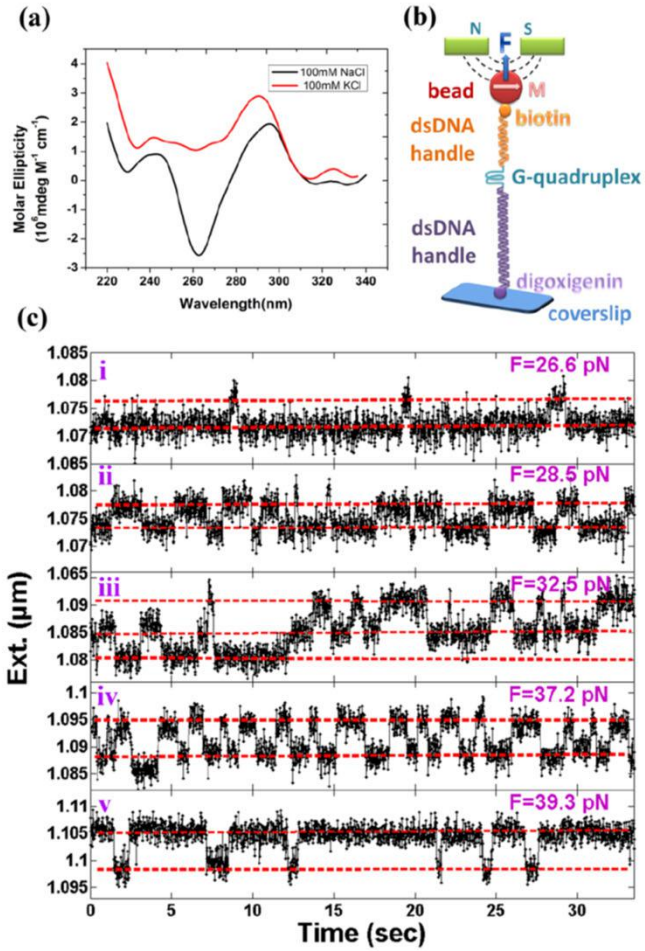


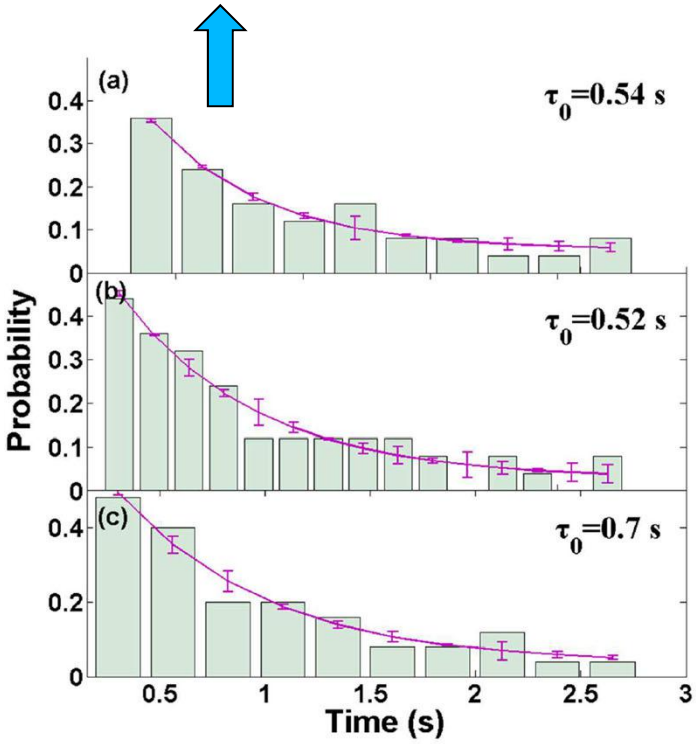
磁镊单分子力谱技术，证实 G4 结构的中间态假说：

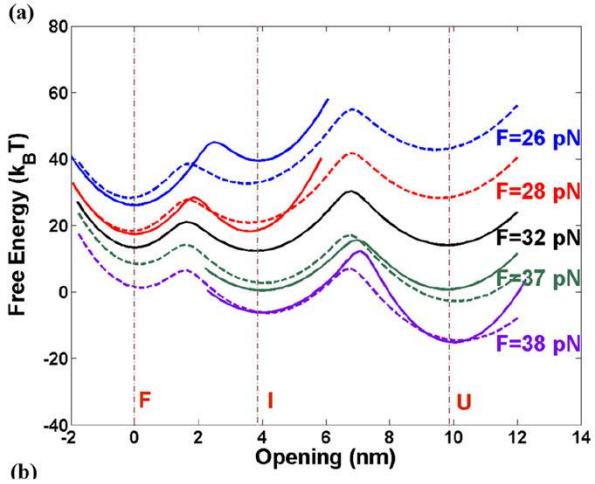




K_{eq}平衡常数是二态系统的驻留时间之比

$$k_B T \ln[K_{eq}] = F\Delta x - (\Delta G^0 + \Delta G_{stre})$$





JACS. dx.doi.org/10.1021/ja4019176

§ Summary & further reading

Summary

- Statistical mechanics for closed system
  - Entropy and Internal energy $S = -k_B \sum_j P_j \ln P_j ; \quad U = \sum_j P_j E_j$
  - Temperature $\frac{1}{T} = \left. \frac{\partial S}{\partial U} \right|_V$
  - Free energy $F = U - TS = -k_B T \ln Z$
  - Boltzmann distribution $P_j = e^{-\beta E_j} / Z \qquad Z = \sum_j e^{-\beta E_j}$
  - Gibbs distribution

$$p\left(E_s^{(i)}, N_s^{(i)}\right) \propto \mathrm{e}^{-\beta\left(E_s^{(i)} - \mu N_s^{(i)}\right)} = \frac{\mathrm{e}^{-\beta\left(E_s^{(i)} - \mu N_s^{(i)}\right)}}{\mathrm{Z}}$$

$$\mathcal{Z} = \sum_i e^{-\beta\left(E_s^{(i)} - N_s^{(i)} \mu\right)}$$

- Simple Applications
  - Ligand-receptor

$$p_{bound} = \frac{(c/c_0)\mathrm{e}^{-\beta\Delta\varepsilon}}{1+(c/c_0)\mathrm{e}^{-\beta\Delta\varepsilon}}$$

  - Gene express (simple model)

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

  - Two-state model for L-R binding

$$\langle N\rangle = \frac{(c/c_0)\mathrm{e}^{-\beta\Delta\varepsilon}}{1+(c/c_0)\mathrm{e}^{-\beta\Delta\varepsilon}}$$

$$\Delta\varepsilon = \varepsilon_b - \mu_0$$

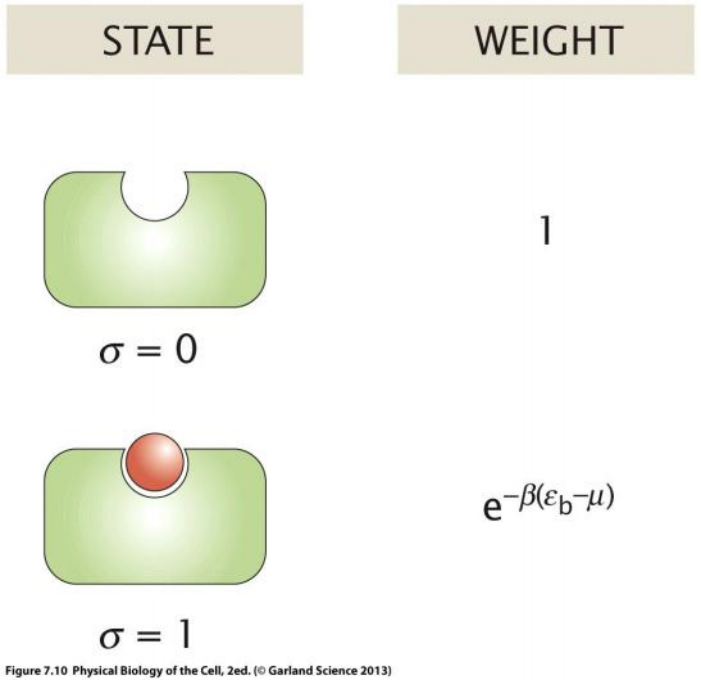


Figure 7.10 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Further reading

- Phillips et al., Physical Biology of the Cell, ch6-7
- Jaynes (1989) Papers on Probability and Statistics
- Imai (1990) Precision determination and Adair scheme analysis of oxygen equilibrium curves of concentrated hemoglobin solution, Biophys. Chem. **37**, 1.