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
➔ \( \Omega \) … 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

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

Figure 6.2 Physical Biology of the Cell (© Garland Science 2009)
What is the occurrence probability of each microstate?
Example: A two-state system (ion channel: open versus closed)

(A) 10 ms
2 pA
CLOSED
OPEN

(B) STATE  ENERGY  WEIGHT

\[ \varepsilon_{\text{closed}} \quad e^{-\beta \varepsilon_{\text{closed}}} \]

\[ \varepsilon_{\text{open}} \quad e^{-\beta \varepsilon_{\text{open}}} \]

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, \( p_{\text{open}} \) and \( p_{\text{closed}} \)

- what determines these probabilities?
  
  *energies of individual microstates, \( \varepsilon_{\text{open}} \) and \( \varepsilon_{\text{closed}} \)*

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
\[ Z = \sum_i \exp(-E_i/k_B T) \quad \text{... sum over all microstates} \]

Why do we need the probabilities and the partition function?

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

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

\[ \langle E \rangle = -Z^{-1} \frac{\partial Z}{\partial \beta} = -\frac{\partial (\ln Z)}{\partial \beta} \]
Ligand-Receptor Binding:

- binding of oxygen to hemoglobin
- binding of transcription factors to DNA

How do we calculate the probability of receptor binding?

\[
p_{\text{bound}} = \frac{\sum_{\text{states}} \left( \begin{array}{c} \vdots \\ \end{array} \right) }{\sum_{\text{states}} \left( \begin{array}{c} \vdots \\ \end{array} \right) + \sum_{\text{states}} \left( \begin{array}{c} \vdots \\ \end{array} \right) }
\]

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*

\[
\begin{align*}
\text{STATE} & \\
(A) & \\
\text{ENERGY} & = L\varepsilon_{\text{sol}} \\
\text{MULTIPlicity} & \approx \frac{\Omega!}{L!(\Omega-L)!} \approx \frac{\Omega^L}{L!} \\
\text{WEIGHT} & = \frac{\Omega^L}{L!} e^{-\beta L\varepsilon_{\text{sol}}}
\end{align*}
\]

\[
\begin{align*}
\text{STATE} & \\
(B) & \\
\text{ENERGY} & = (L-1)\varepsilon_{\text{sol}} + \varepsilon_b \\
\text{MULTIPlicity} & \approx \frac{\Omega!}{(L-1)!(\Omega-L+1)!} \approx \frac{\Omega^{L-1}}{(L-1)!} \\
\text{WEIGHT} & = \frac{\Omega^{L-1}}{(L-1)!} e^{-\beta[(L-1)\varepsilon_{\text{sol}} + \varepsilon_b]}
\end{align*}
\]

Figure 6.4 Physical Biology of the Cell (© Garland Science 2009)
Weight for a situation in which a receptor is bound:

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

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

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

weight (bound) = \(\Omega!/[(L - 1)! (\Omega - L + 1)!] \exp[-\beta \varepsilon - \beta (L-1)\varepsilon_{s_l}]\)

weight (unbound) = \(\Omega!/[L! (\Omega - L)!] \exp[-\beta L\varepsilon_{s_l}]\)

Partition function:

\[
Z(L,\Omega) = \text{weight (bound)} + \text{weight (unbound)}
\]
Useful approximation for the case $L \ll \Omega$:

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

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 $p_{\text{bund}}$ as:

$$p_{\text{bund}} = \frac{(L/\Omega) \exp(-\beta \Delta \varepsilon)}{[1 + (L/\Omega) \exp(-\beta \Delta \varepsilon)]}$$

$$p_{\text{bund}} = \frac{(c/c_0) \exp(-\beta \Delta \varepsilon)}{[1 + (c/c_0) \exp(-\beta \Delta \varepsilon)]}$$
Classical result: a competition between energetic and entropic contributions to the free energy: $c/c_0 = \frac{1}{2} \ldots$ half occupancy
Statistical Mechanics of Gene Expression:
RNA polymerase binding at promotor sites

Cells can control transcription and translation: revised central dogma
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).

a microscopy image of transcription

Figure 3.9 Physical Biology of the Cell (© Garland Science 2009)
Experimental evidence: thousands of RNA polymerase molecules in *E. coli* bound to the DNA promoter sites
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:

$$Z_{NS}(P, N_{NS}) = \frac{N_{NS}!}{P!(N_{NS}-P)!} \exp(-\beta P \varepsilon_{NS}^{pd})$$

![Diagram of RNA polymerase binding to DNA](image)
The total partition function is a sum of two parts:

\[ Z(P, N_N) = Z_N(P, N_N) + Z_N(P - 1, N_N) \exp(-\beta \varepsilon^S_{pl}) \]

Probability of one RNAP bound to the promoter site is:

\[ p_{bound} = \frac{\sum \text{states} \left( \begin{array}{c} \text{states} \\
\text{promoter} \end{array} \right)}{\sum \text{states} \left( \begin{array}{c} \text{states} \\
\end{array} \right) + \sum \text{states} \left( \begin{array}{c} \text{states} \\
\end{array} \right)} \]
Figure 6.11 Physical Biology of the Cell (© Garland Science 2009)
\[
p_{\text{bind}} = \frac{Z_{NS}(P-1,N_{NS}) \exp(-\beta \epsilon^S_{pl})}{[Z_{NS}(P,N_{NS}) + Z_{NS}(P-1,N_{NS}) \exp(-\beta \epsilon^S_{pl})]} = [1 + N_{NS}/P \exp(\beta \Delta \epsilon_{pl})]^{-1}
\]

\[
\Delta \epsilon_{pl} = \epsilon^S_{pl} - \epsilon^NS_{pl}
\]

The more negative the difference \(\Delta \epsilon_{pl}\), 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:

\[
p(E_s^I)/p(E_s^II) = \frac{W_r(E_{tot} - E_s^I)}{W_r(E_{tot} - E_s^II)}
\]
\( W_{\text{tot}} (E_{\text{tot}} - E_s) = 1 \times W_r (E_{\text{tot}} - E_s) \)

One state of the system \( x \) all possible States of the reservoir

\[ S = k_B \ln W \]

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

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

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

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 macrortostate \( X \)!