Lecture 6: Proteins; entropy rules

Goal: Introduce Boltzmann distribution, probability of microstate

- Ligand-receptor binding
- Gene regulation
- Cooperativity

PBOC Chapter 6.1.1, 6.1.2, 6.4
(except 6.4.4)

Statistical mechanics for biophysics

Numbers:
RNA polymerase molecules in the nucleus
Ligands near cell surface

What can we answer with these models?
Determine the probability of finding the system in a particular (energy) state.
Calculate the average values of observables.

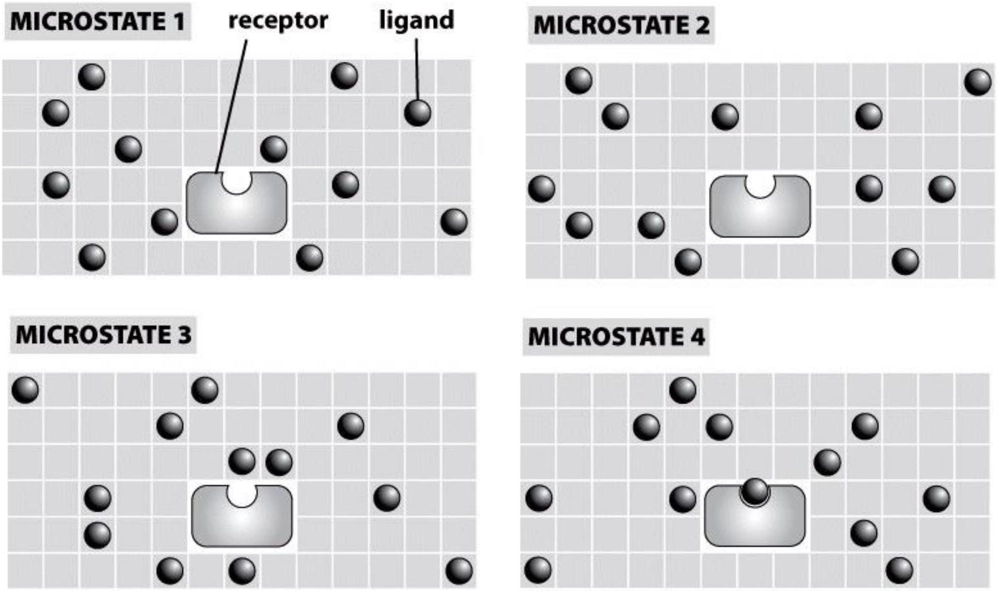
Statistical mechanics for biophysics

Previously (Lecture 3):

Microstates

Definition: a ***microstate*** is a microscopic arrangement of the constituents of a system

Example: Ligand binding to a receptor protein



Lattice model

L ligands

$\boldsymbol{\Omega}$ boxes

max. one ligand per box

energy ε_b of a bound ligand

energy ε_{sol} of a ligand in solution

Statistical mechanics for biophysics

Microstates

Suppose a system can exist in states with energies E_i.
What is the probability of finding the system in a given state?

Boltzmann distribution, probability of finding the system in a microstate with energy E_i *(derivation, Section 6.1.3)*

$$p(E_i) = \frac{1}{Z} e^{-E_i/k_B T}$$

Partition function, normalization factor so that $\sum_{i=1}^{N} p(E_i) = 1$

$$Z = \sum_{i=1}^{N} e^{-E_i/k_B T}$$

Statistical mechanics for biophysics

Microstates

Suppose a system can exist in states with energies E_i.
What is the average energy of the system?

The average energy is the (probability) weighted mean of the energies of the states:

$$\langle E \rangle = \sum_{i=1}^{N} E_i p(E_i) = \frac{1}{Z} \sum_{i=1}^{N} E_i e^{-\beta E_i}$$

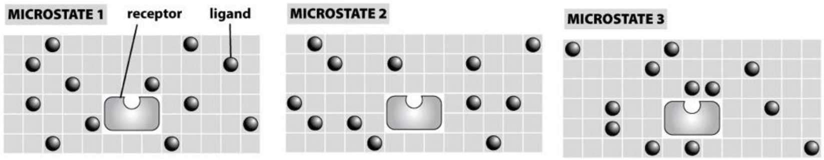
$$= -\frac{1}{Z} \frac{\partial Z}{\partial \beta} = -\frac{\partial}{\partial \beta} (lnZ)$$

Statistical mechanics for biophysics

Example: Ligand binding
Lattice model
L ligands
Ω boxes
max. one ligand per box

Microstates: multiplicity (Lecture 3)

Microstates with receptor unoccupied



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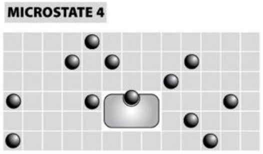
$$\text{number of microstates} = \frac{\Omega!}{L!(\Omega-L)!}$$

Microstates with receptor occupied



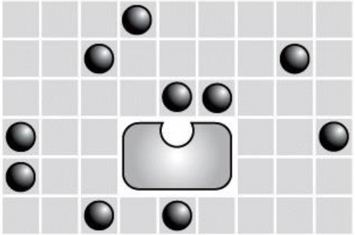
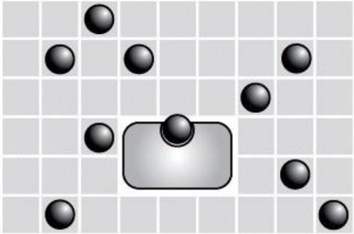
. . .

number of microstates?

Statistical mechanics for biophysics

Example: Ligand binding to receptor protein

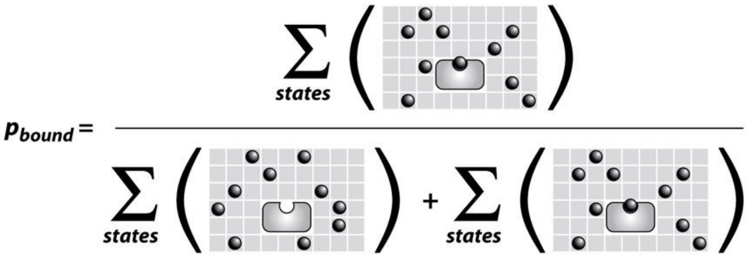
Microstates: energy, weight

	STATE	ENERGY	MULTIPLICITY	WEIGHT multiplicity x Boltzmann weight "partial" partition function
receptor unbound		$L\varepsilon_{sol}$	$\frac{\Omega!}{L!(\Omega-L)!} \approx \frac{\Omega^L}{L!}$ for $\Omega >> L$	$\frac{\Omega^L}{L!} e^{-\beta L\varepsilon_{sol}}$
receptor bound		$(L-1)\varepsilon_{sol} + \varepsilon_b$	$\frac{\Omega!}{(L-1)!(\Omega-L+1)!} \approx \frac{\Omega^{L-1}}{(L-1)!}$	$\frac{\Omega^{L-1}}{(L-1)!} e^{-\beta[(L-1)\varepsilon_{sol} + \varepsilon_b]}$

Statistical mechanics for biophysics

Example: Ligand binding to receptor protein

Microstates: probability



$$= \frac{\frac{\Omega^{L-1}}{(L-1)!} e^{-\beta[(L-1)\varepsilon_{sol}+\varepsilon_b]}}{\frac{\Omega^L}{L!} e^{-\beta L \varepsilon_{sol}} + \frac{\Omega^{L-1}}{(L-1)!} e^{-\beta[(L-1)\varepsilon_{sol}+\varepsilon_b]}}$$

$$= \frac{\frac{L}{\Omega} e^{-\beta[\varepsilon_b - \varepsilon_{sol}]}}{1 + \frac{L}{\Omega} e^{-\beta[\varepsilon_b - \varepsilon_{sol}]}}$$

$$= \frac{\frac{c}{c_0} e^{-\beta \Delta\varepsilon}}{1 + \frac{c}{c_0} e^{-\beta \Delta\varepsilon}}$$

Langmuir isotherm

Hill function of coefficient 1

Define: $\Delta\varepsilon = \varepsilon_b - \varepsilon_{sol}$

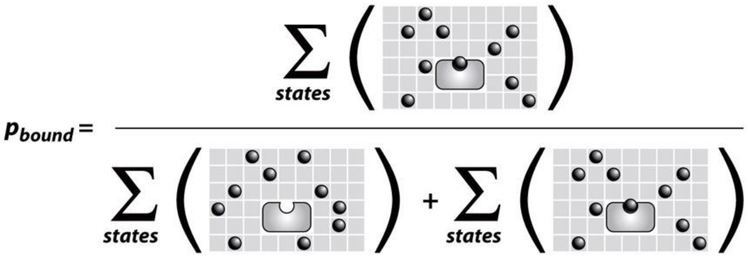
$c(L) = L/V_{box}$

$c(L = \Omega) = c_0 = \Omega/V_{box}$

Statistical mechanics for biophysics

Example: Ligand binding to receptor protein

Microstates: probability



$$= \frac{\frac{c}{c_0} e^{-\beta \Delta \varepsilon}}{1 + \frac{c}{c_0} e^{-\beta \Delta \varepsilon}}$$

$$L + R \rightleftharpoons LR$$

$$K_d = \frac{[L][R]}{[LR]}$$

$$p_{bound} = \frac{[LR]}{[R] + [LR]}$$

$$p_{bound} = \frac{\frac{[L]}{K_d}}{1 + \frac{[L]}{K_d}}$$

Statistical mechanics for biophysics

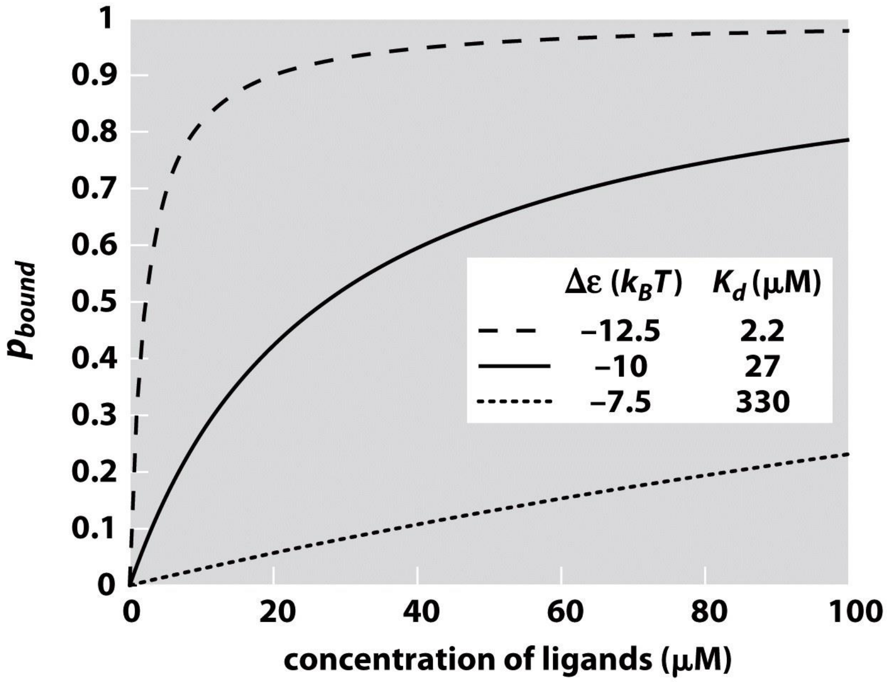
Example: Ligand binding to receptor protein

Estimate: $V_{box} = 1\ \text{nm}^3$

then $c_0 = \frac{\Omega}{V_{box}} = \left(\frac{6\times 10^{23}}{10^{24}}\right)$

$$= 0.6\ M$$

Receptor occupancy

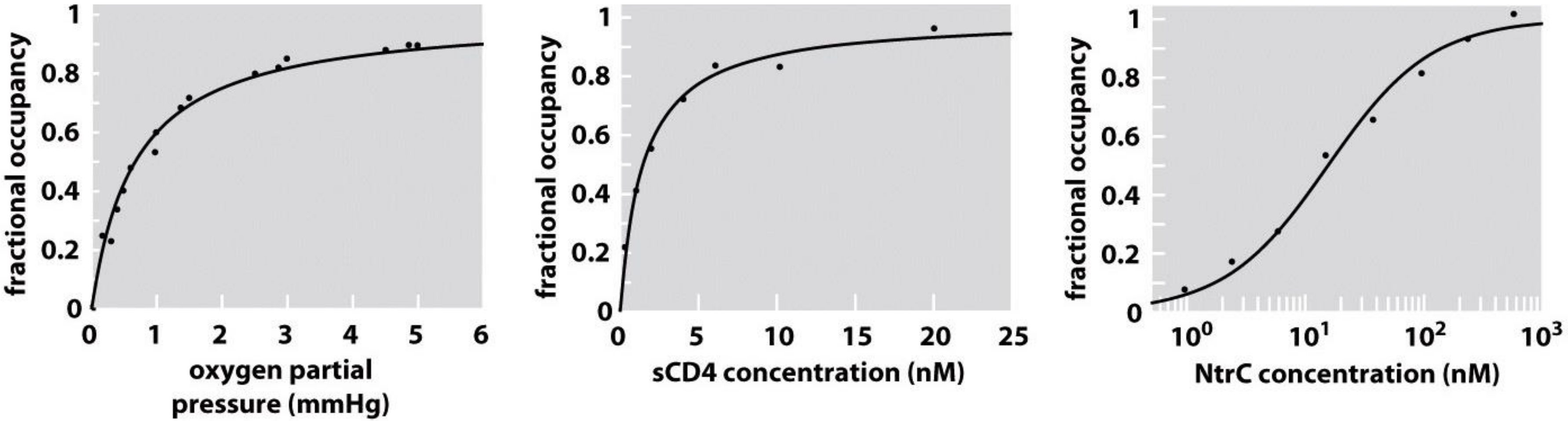


Statistical mechanics for biophysics

Example: Ligand binding to receptor protein

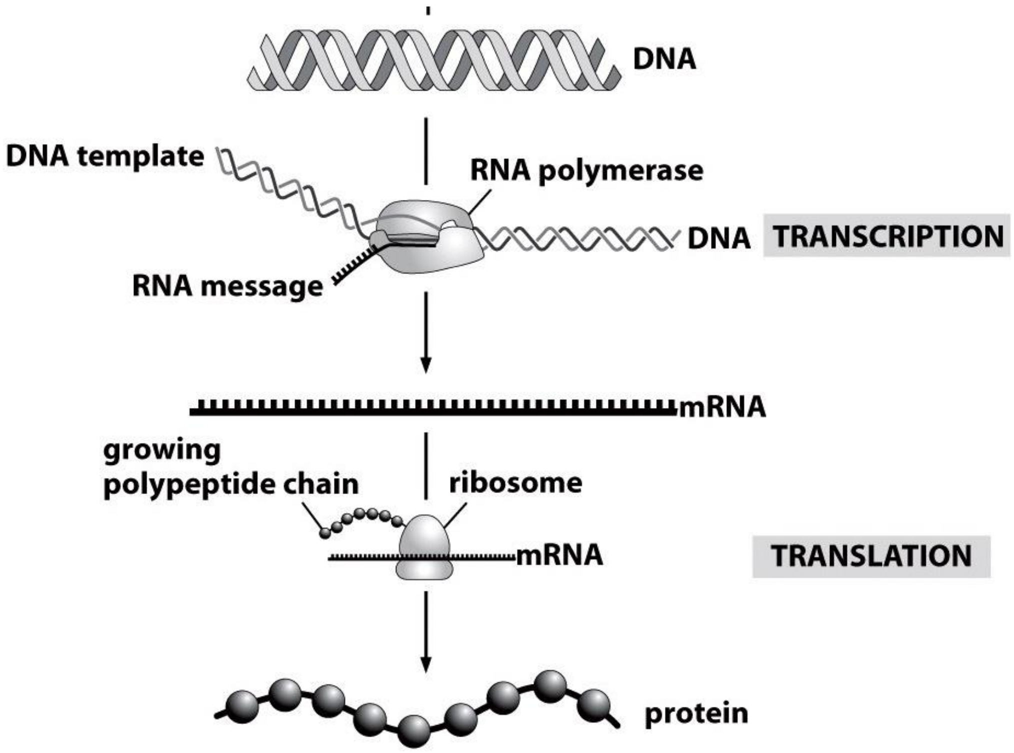
Receptor occupancy

Experimental data



Statistical mechanics for biophysics

Central dogma



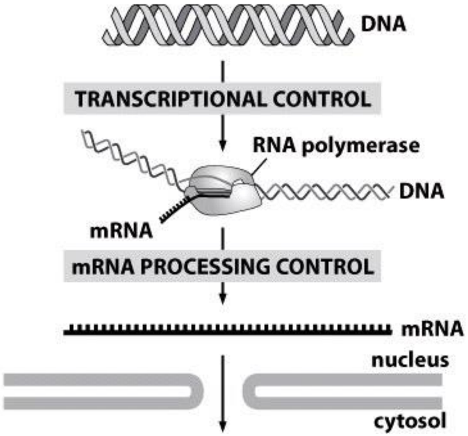
Statistical mechanics for biophysics

How do cells make decisions?

How can different cells in an organism maintain different protein concentrations?

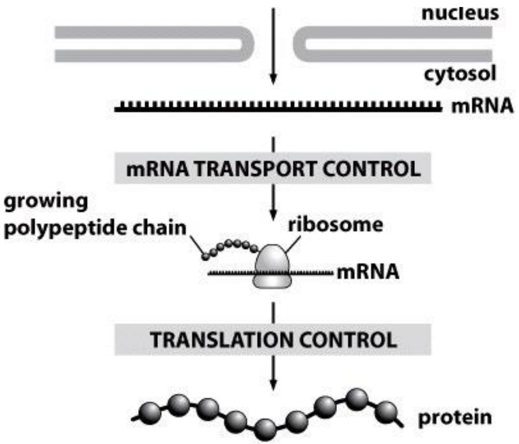
Statistical mechanics for biophysics

Will the cell make a particular mRNA?



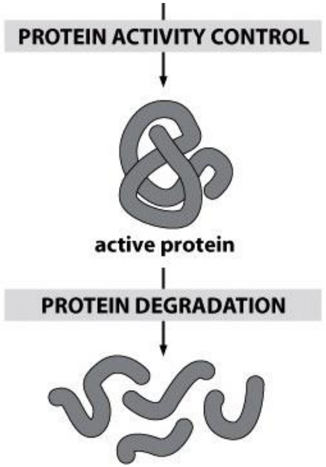
Will an mRNA be processed to become mature?

Will an mRNA be transported to the cytoplasm?



Will an mRNA be translated by the ribosome?

Will a protein exist in an active conformation?

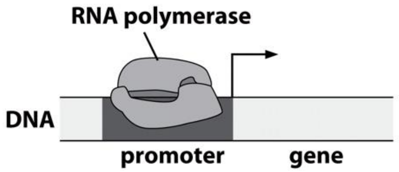


How long will a protein last before being degraded?

Statistical mechanics for biophysics

Will the cell make a particular mRNA?

Example: Transcriptional control



Lattice model

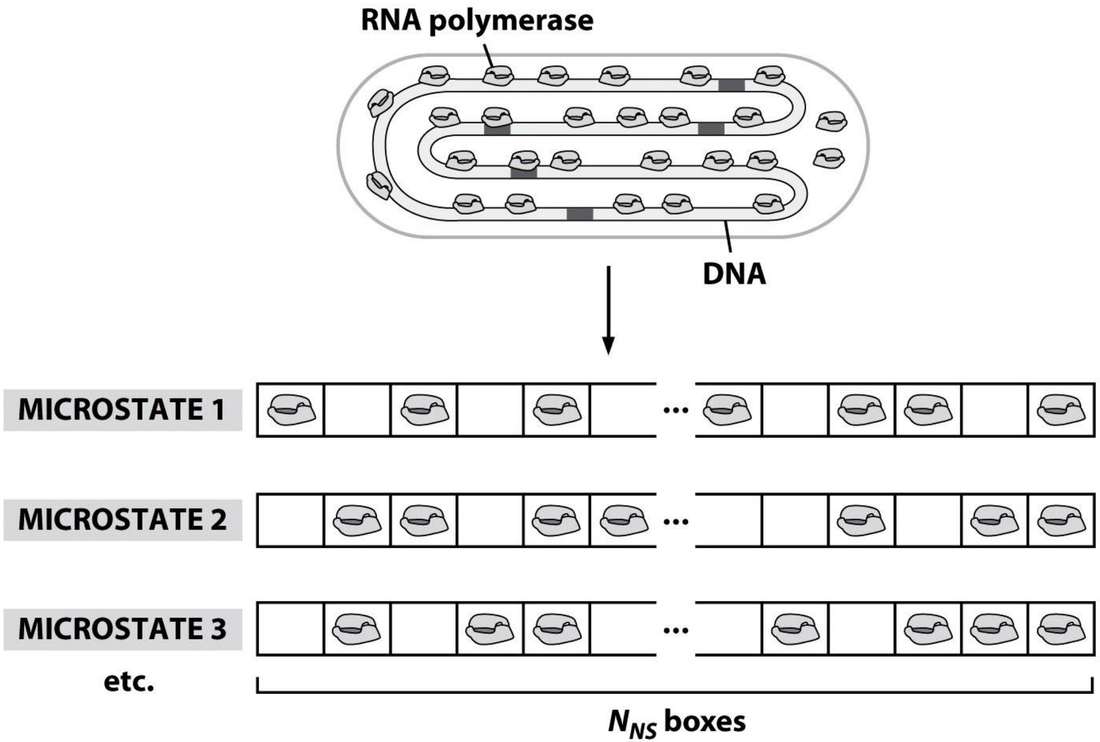
P RNA polymerases

N_{NS} boxes

max. one RNAp per box

assume all are bound

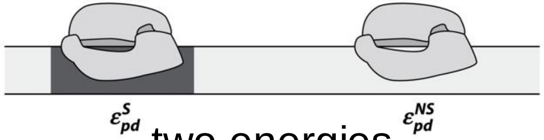
Microstates



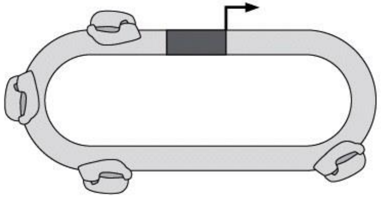
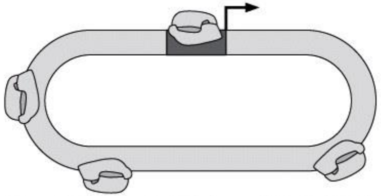
Statistical mechanics for biophysics

Example: Transcriptional control

Microstates



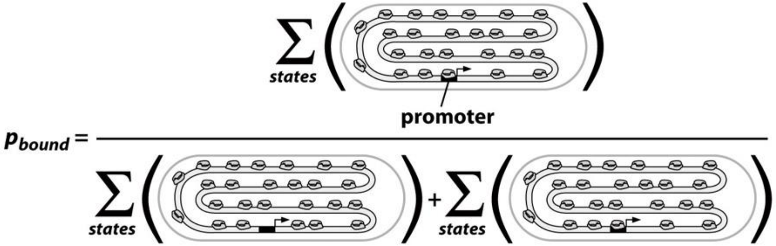
two energies

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

Statistical mechanics for biophysics

Example: Transcriptional control

Microstates: probability



$$= \frac{\frac{N_{NS}^{P-1}}{(P-1)!} e^{-\beta[(P-1)\varepsilon_{NS}+\varepsilon_S]}}{\frac{N_{NS}^{P}}{P!} e^{-\beta P \varepsilon_{NS}} + \frac{N_{NS}^{P-1}}{(P-1)!} e^{-\beta[(P-1)\varepsilon_{NS}+\varepsilon_S]}}$$

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

Define: $\Delta\varepsilon = \varepsilon_S - \varepsilon_{NS}$

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

Langmuir isotherm

Hill function of coefficient 1

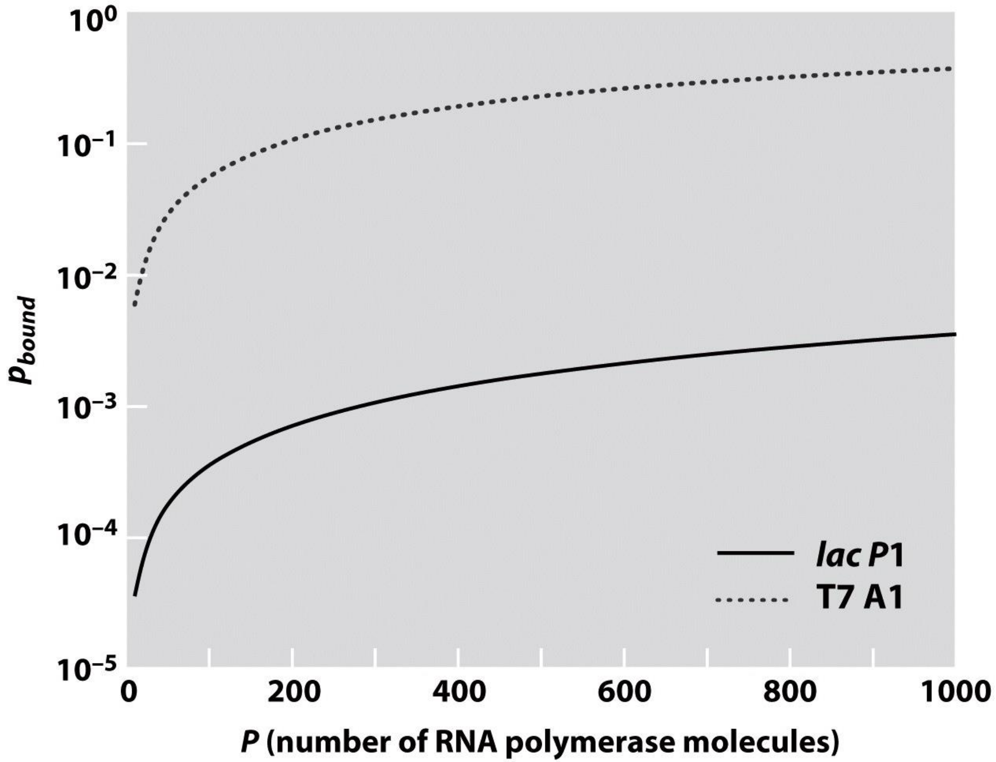
Statistical mechanics for biophysics

Example: Transcriptional control

RNA polymerase occupancy

Estimate:
$\Delta\varepsilon = -2.9\ k_B T$ E. coli
$\Delta\varepsilon = -8.1\ k_B T$ bacteriophage T7

~5000 RNA polymerase in E. coli



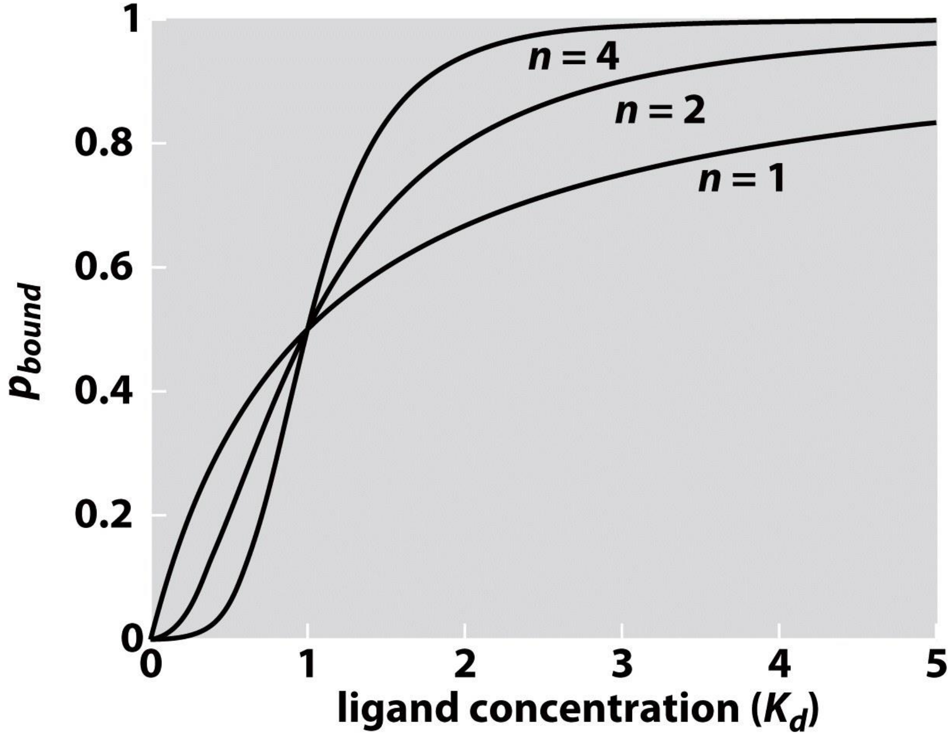
$Cooperativity$

Analog signal → digital output

Statistical mechanics for biophysics

Cooperativity

Binding curves with different Hill coefficients



Lecture 6: Entropy rules

Summary

Lecture 7: Two-state system, ion channels

Goal: Statistical mechanics modeling. Compute the probability of microstates, including applied forces.

- Two-state system
- Mechanosensitive ion channels

PBOC Chapter 7.1.2, 11.5