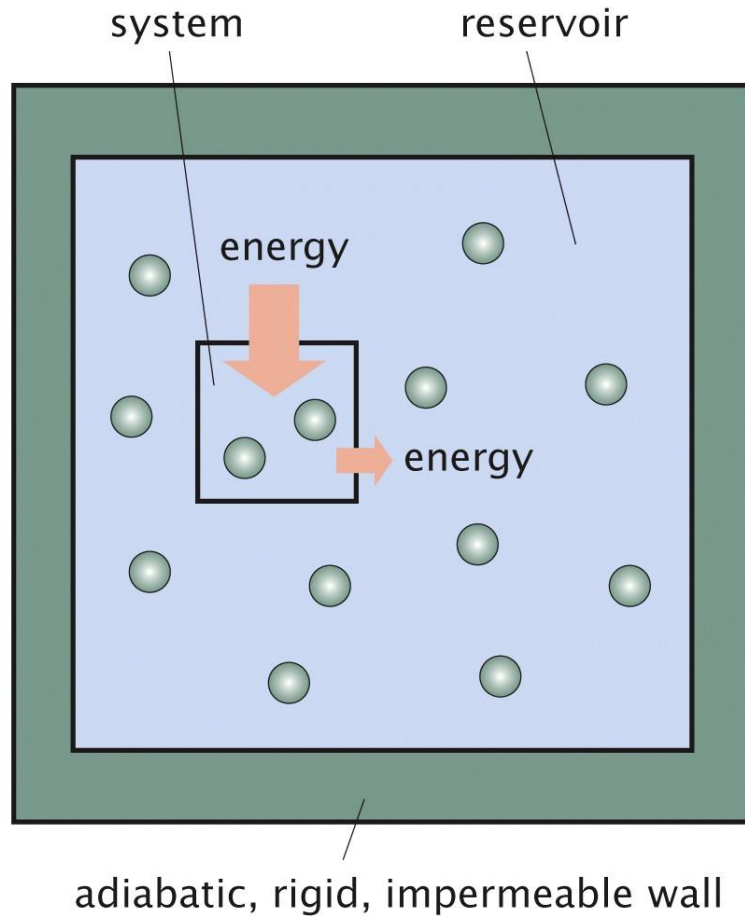


Topic 3: Probability Theory and Boltzmann Distribution

The Boltzmann Distribution:



So far we've been talking about Ideal gases, but what about real systems

Consider a small system of particles that finds itself in a large thermal reservoir, that is at fixed temperature

We want to calculate statistical properties of this system

Want to find the probability of finding the system in each of its possible states

We will derive the Boltzmann distribution

Figure 6.14 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Microstates:

What we mean, is that the small system can be in a variety of possible configurations, each with its own associated energy E .

Given that this system is in contact with the thermal reservoir, what is the likelihood of observing a particular configuration?

we call these configurations of the small system, microstates

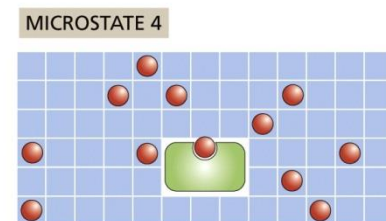
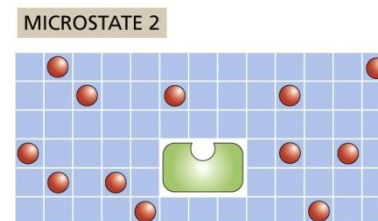
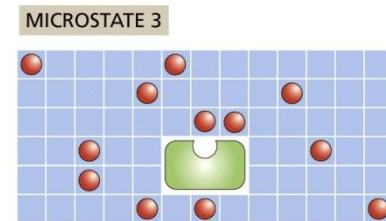
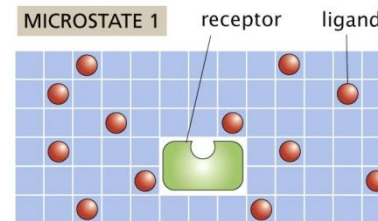
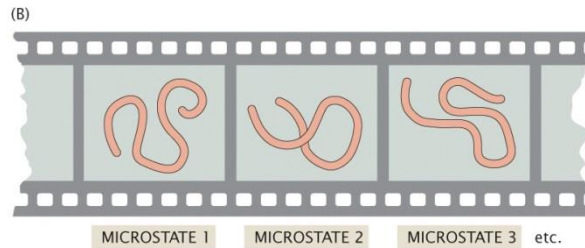


Figure 6.2 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

need to be able to count these microstates

Boltzmann distribution derivation

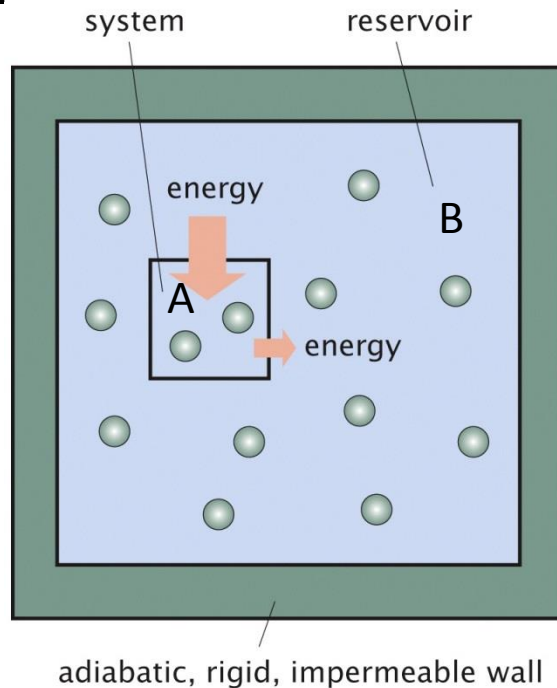


Figure 6.14 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Both systems, A and B are at temperature T

Total energy is constant: $E_{tot} = E_A + E_B$

Equilibrium: every state in the combined system has energy E_{tot} and so has the same probability of occurring

Using this postulate, what does it imply for $P(E_A)$?

For A, in a state with energy E_A , how many states in system B are there? (the one that has the most states in B will be the most likely to be observed)

We know the entropy in B:

$$S(E_B) = k_B \log(\Omega(E_B)) \quad \text{thus the number of states in B is } \Omega(E_B) = \exp\left(\frac{S(E_B)}{k_B}\right)$$

Boltzmann distribution derivation

But we know that $E_B = E_{tot} - E_A$, so it depends on the energy in A, so rewrite

$$\Omega(E_{tot} - E_A) = \exp(S_B(E_{tot} - E_A))$$

Thus the # of states in B depends on what state A is in.

• So prob of \textcircled{A} being in E_A is $\sim P_0 \cdot (\# \text{ of B states})$

$$\text{or } P(E_A) \propto P_0 \Omega(E_{tot} - E_A) = P_0 e^{S_B(E_{tot} - E_A)/k_B}$$

• Since $E_A \ll E_{tot}$, we can expand $S_B(E_{tot} - E_A)$:

$$S_B(E_{tot} - E_A) \approx S_B(E_{tot}) - E_A \frac{dS_B}{dE_B} \leftarrow \text{temperature, } \frac{1}{T_B}$$

• So

$$P(E_A) \propto \left(P_0 e^{S_B(E_{tot})/k_B} \right) e^{-E_A/k_B T_B}$$

↑
indep of E_A

or

$$P(E_A) = A e^{-E_A/k_B T}$$

Boltzmann distribution normalization

$$P(E_n) = A e^{-E_n/k_B T}$$

Find A by normalizing. $\sum_{E_n} P(E_n) = 1$

$$\Rightarrow A = \left(\sum_{E_n} e^{-E_n/k_B T} \right)^{-1}$$

or

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

where

$$Z = \sum_{E_n} e^{-E_n/k_B T}$$

$Z \equiv$ Partition function.

$$P(E_n) = \frac{1}{Z} e^{-E_n/k_B T} \equiv \text{Boltzmann distribution}$$

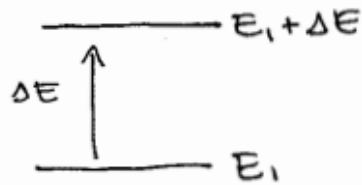
$$P(E) = \frac{1}{Z} \exp\left(-\frac{E}{k_B T}\right) \text{ where } Z = \sum_E \exp\left(-\frac{E}{k_B T}\right)$$

commit this equation to memory – you will use it lots

Thus for a system at temperature T , the probability of a state with energy, E is given by the above distribution. The rest is just application of this equation.

Two state systems:

Two-state System: Suppose \textcircled{A} can exist in 2 states

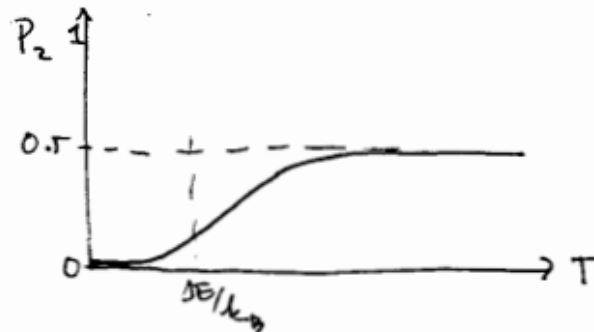
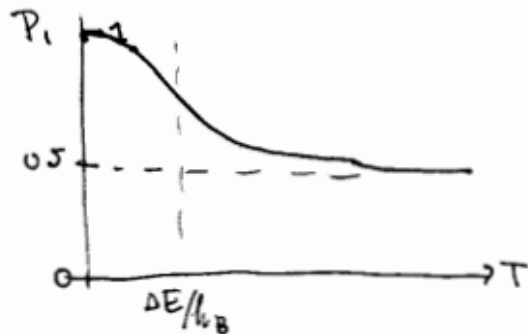


$$\textcircled{1} \frac{P_1}{P_2} = \frac{e^{-E_1/kT}}{e^{-(E_1 + \Delta E)/kT}} = e^{\Delta E/kT}$$

$$\textcircled{2} P_1 + P_2 = 1$$

combining $\textcircled{1}$ & $\textcircled{2}$ gives:

$$P_1 = \frac{1}{1 + e^{-\Delta E/kT}} \quad ; \quad P_2 = \frac{1}{1 + e^{\Delta E/kT}}$$



- @ low T , system is in lowest energy state, E_1 .
- as T rises, both states become equally likely.

Two state system: an ion channel

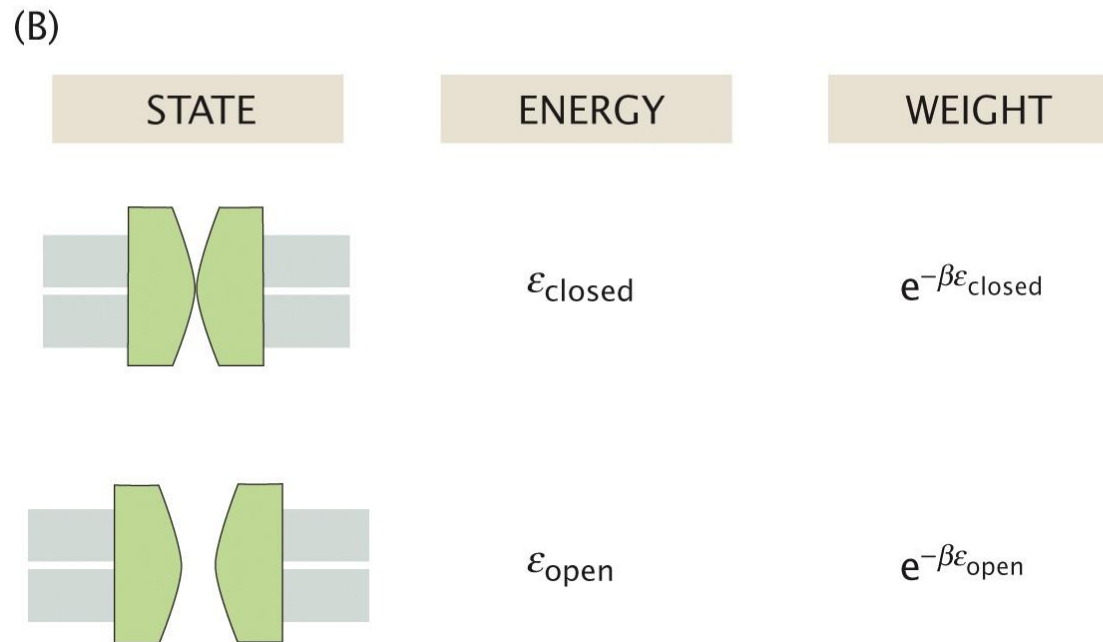
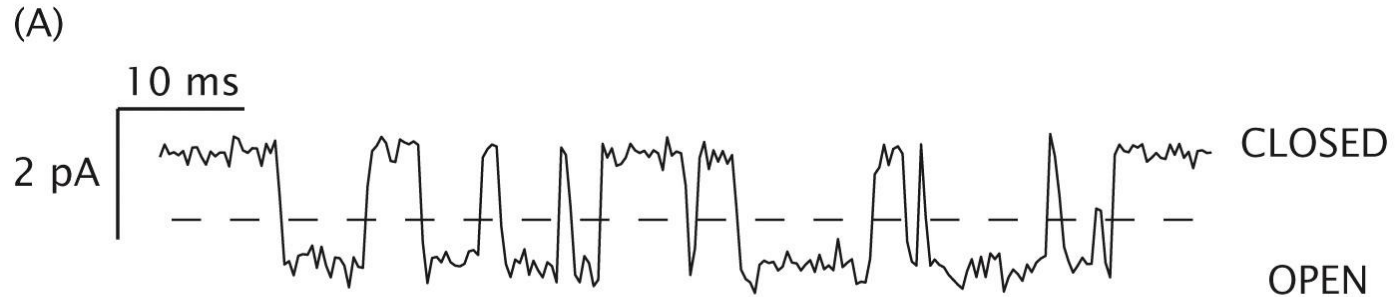
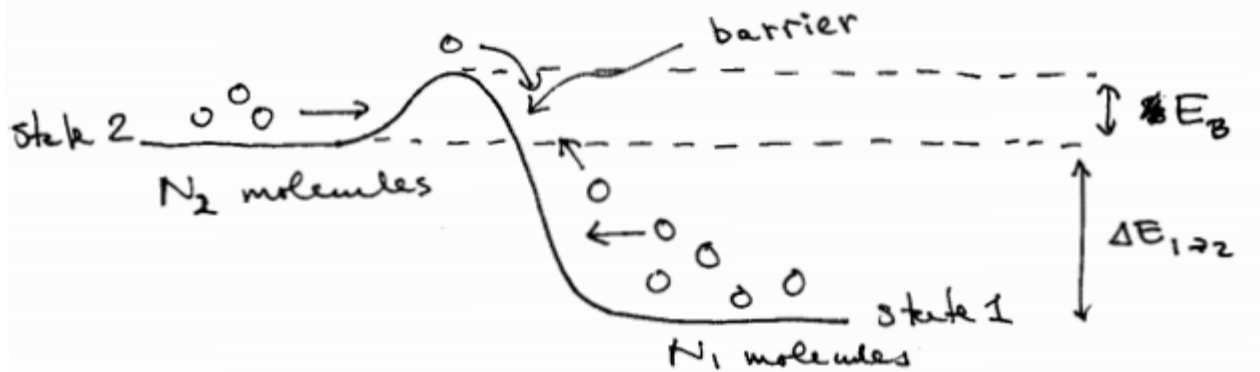


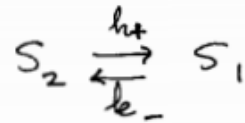
Figure 6.3 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

$$\frac{t_c}{t_o} = \exp\left(-\frac{\epsilon_c}{kT}\right) / \exp\left(-\frac{\epsilon_o}{kT}\right)$$

Boltzmann and chemical kinetics:



chemical equilibrium occurs when the flow from state 1 to state 2 is the same as the flow from state 2 to state 1. What does this imply?



k_+ \equiv prob of going from S_2 to S_1 (chance of going over barrier)/unit time

so $k_+ = C e^{-E_B/kT}$ ← chance of having an energy that would get you over the barrier

↑
constant

• So assume the # of N_2 molecules going to S_1 is

$$N_2 k_+ = N_2 C e^{-E_B/kT}$$

Chemical equilibrium:

- What about $S_1 \rightarrow S_2$? To go from $S_1 \rightarrow S_2$ requires going over a barrier of $\Delta E = \Delta E_{1 \rightarrow 2} + E_B$
so

$$k_- = c e^{-(\Delta E_{12} + E_B)/kT}$$

- # of N_1 molecules making transition $S_1 \rightarrow S_2$

$$N_1 k_- = N_1 c e^{-(\Delta E + E_B)/kT}$$

- Equilibrium: $N_2 k_+ = N_1 k_-$

$$\text{or } \frac{N_{2,eq}}{N_{1,eq}} = e^{-\Delta E_{12}/kT} \equiv \frac{P_2}{P_1}$$

So at equilibrium the distribution of particles only depends on the energy difference between the states.

What happened to the energy barrier? It serves to set how long it takes to reach equilibrium. Larger the barrier, the longer it will take to reach equilibrium.

Dwell times:

We've just found the likelihood of being in each state, but on average how long will you spend in each state? this is known as the dwell time.

What are the distribution of dwell times?

$P_{2 \rightarrow 1}(t) \equiv$ the probability that you stay in state 2 for a time, t

Start: ① @ time t there are $N(t)$ molecules in S_2

② after a time dt , $-k_+ dt N(t)$ will have left

so

$$N(t+dt) = (1 - k_+ dt) N(t) \quad (\text{with } N(0) = N_0)$$

solve:

$$N(t) = N_0 e^{-k_+ t}$$

$$P_{2 \rightarrow 1}(t) dt = (\text{prob of surviving in } S_2 \text{ till } t) (\text{prob of jumping in } dt)$$

or

$$P_{2 \rightarrow 1}(t) dt = \left(\frac{N(t)}{N_0} \right) (k_+ dt)$$

exponential distribution

so

$$P_{2 \rightarrow 1}(t) = k_+ e^{-k_+ t}$$

Dwell times:

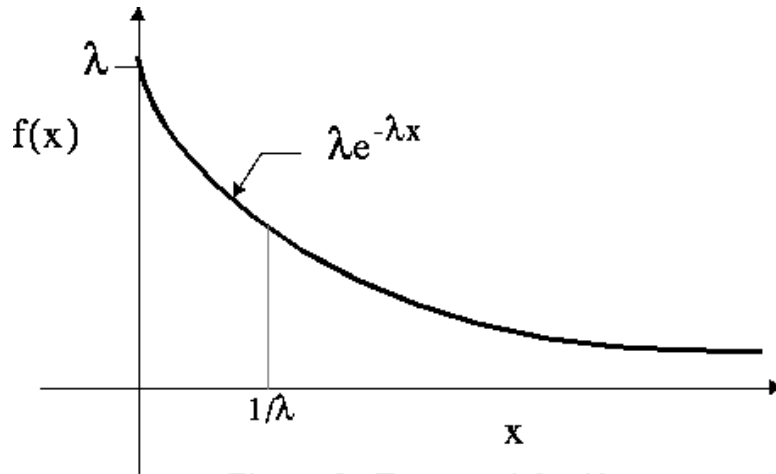


Figure 6. Exponential pdf

So dwell times are distributed exponentially

$$P_{2 \rightarrow 1}(t) = k_+ e^{-k_+ t}$$

Many reactions occur quickly, but some are very slow

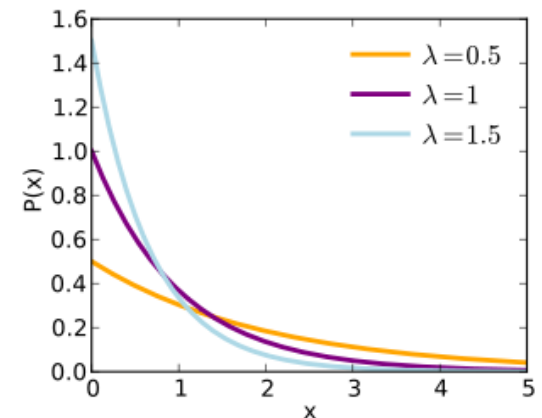
The energy barrier affects the rate. From Boltzmann

rate ($2 \rightarrow 1$) = (attempt rate) x (probability of jumping barrier from $1 \rightarrow 2$)

or

$$k_+ = v \exp\left(-\frac{E_B}{k_B T}\right)$$

so larger barrier \rightarrow slower rate and longer dwell times



Generalizing to systems with degeneracies

Previously, we assumed that the small system had states with energy E , and these states had no degeneracy (i.e. there is only one configuration associated with each energy E).

But what if there are multiple configurations that have the same energy E ?


E_3 ————— # of states, Ω_3

E_2 ————— # of states, Ω_2

E_1 ————— # of states, Ω_1

entropy, S_1

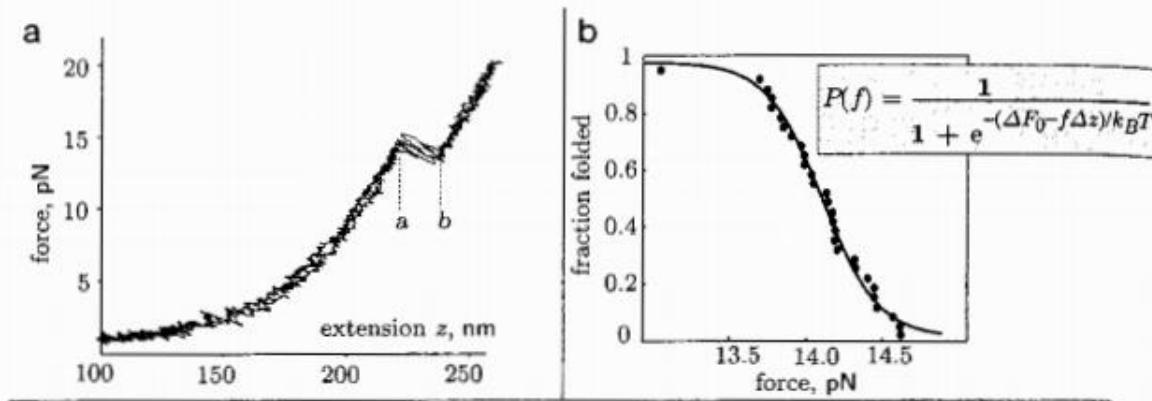
Use Boltzmann to calculate, probability of state 1, etc.

$$P_1 = \frac{\Omega_1 \exp\left(-\frac{E_1}{kT}\right)}{\Omega_1 \exp\left(-\frac{E_1}{kT}\right) + \Omega_2 \exp\left(-\frac{E_2}{kT}\right) + \Omega_3 \exp\left(-\frac{E_3}{kT}\right) + \dots} = \frac{\exp\left[-\frac{1}{kT} (E_1 - kT \log \Omega_1)\right]}{\dots}$$


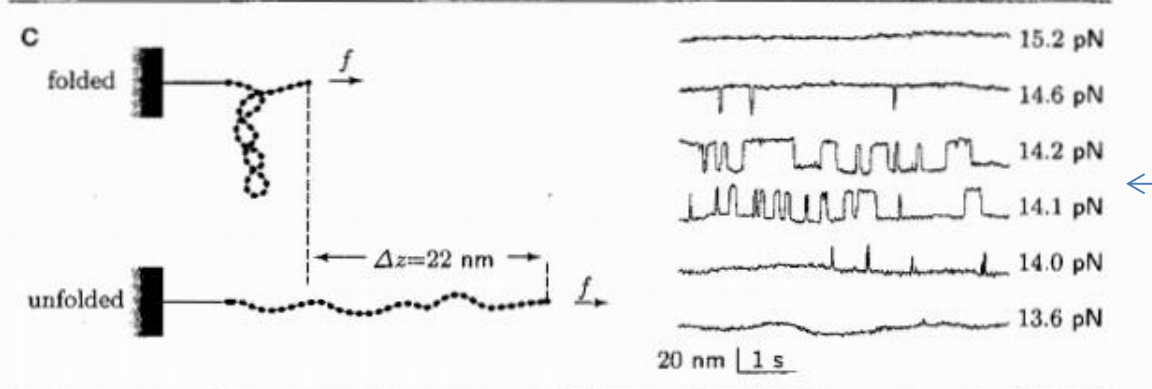
so

$$P_i = \frac{1}{Z} \exp\left(-\frac{G_i}{kT}\right) \text{ where } Z = \sum_i \exp\left(-\frac{G_i}{kT}\right) \text{ and } G_i = E_i - TS_i$$

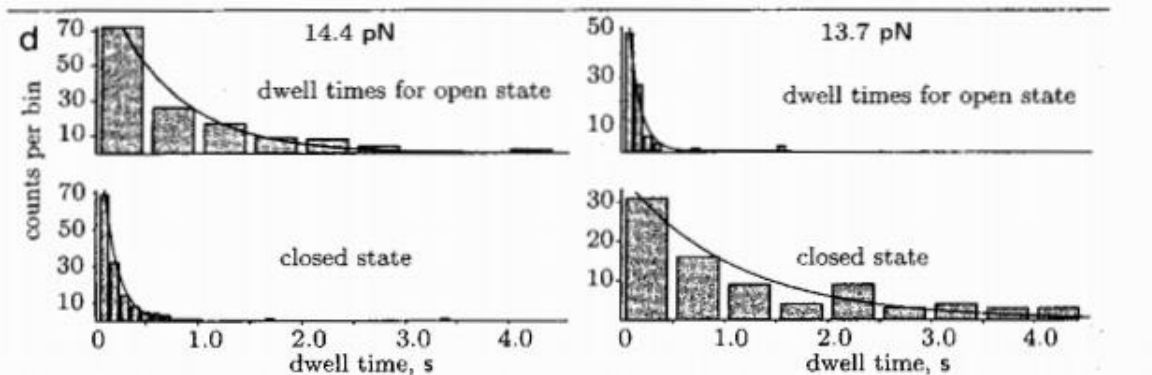
Application to RNA folding



Using an optical tweezer, the Bustamante lab looked at how a single RNA molecule unfolded under different applied forces



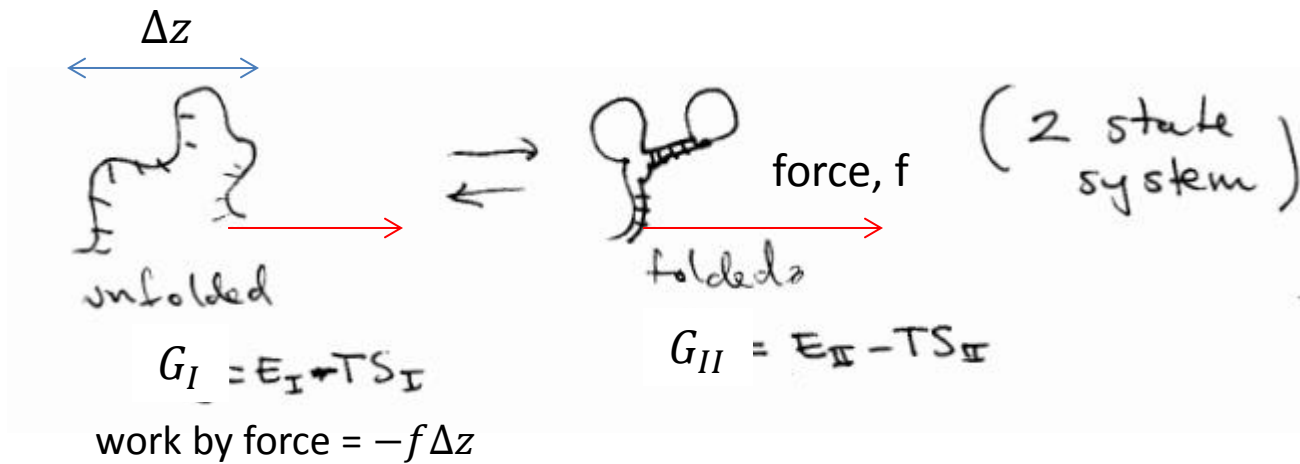
different forces



Measured the probability of being folded

Measured dwell times

Application to RNA folding



The optical trap does work when the RNA unfolds a distance, Δz . So the free energy difference between the unfolded and folded in the presence of a force is:

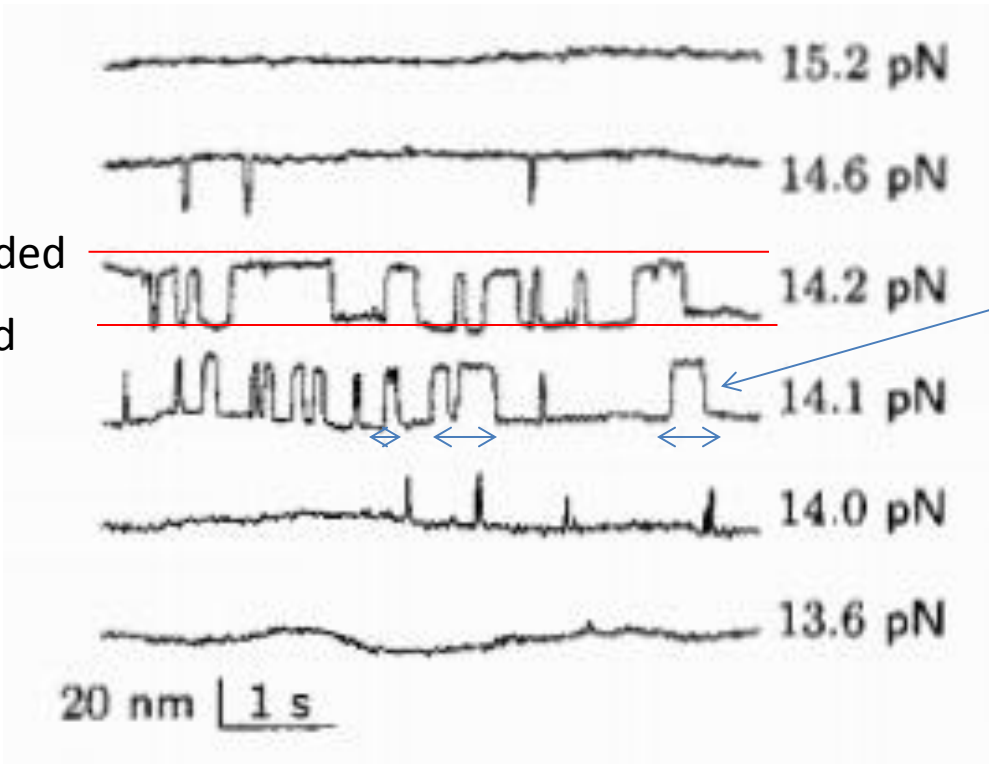
$$\Delta G = G_I - G_{II} - f\Delta z = \Delta G_0 - f\Delta z$$

So the probability of being folded is:

$$P_{II} = \frac{\exp\left(-\frac{G_{II}}{kT}\right)}{\exp\left(-\frac{G_{II}}{kT}\right) + \exp\left(-\frac{G_I - f\Delta z}{kT}\right)} = \frac{1}{1 + \exp\left(-\frac{\Delta G_0 - f\Delta z}{kT}\right)}$$

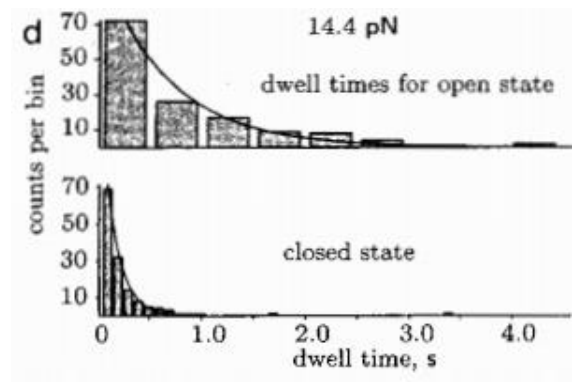
RNA folding dwell times:

unfolded
folded

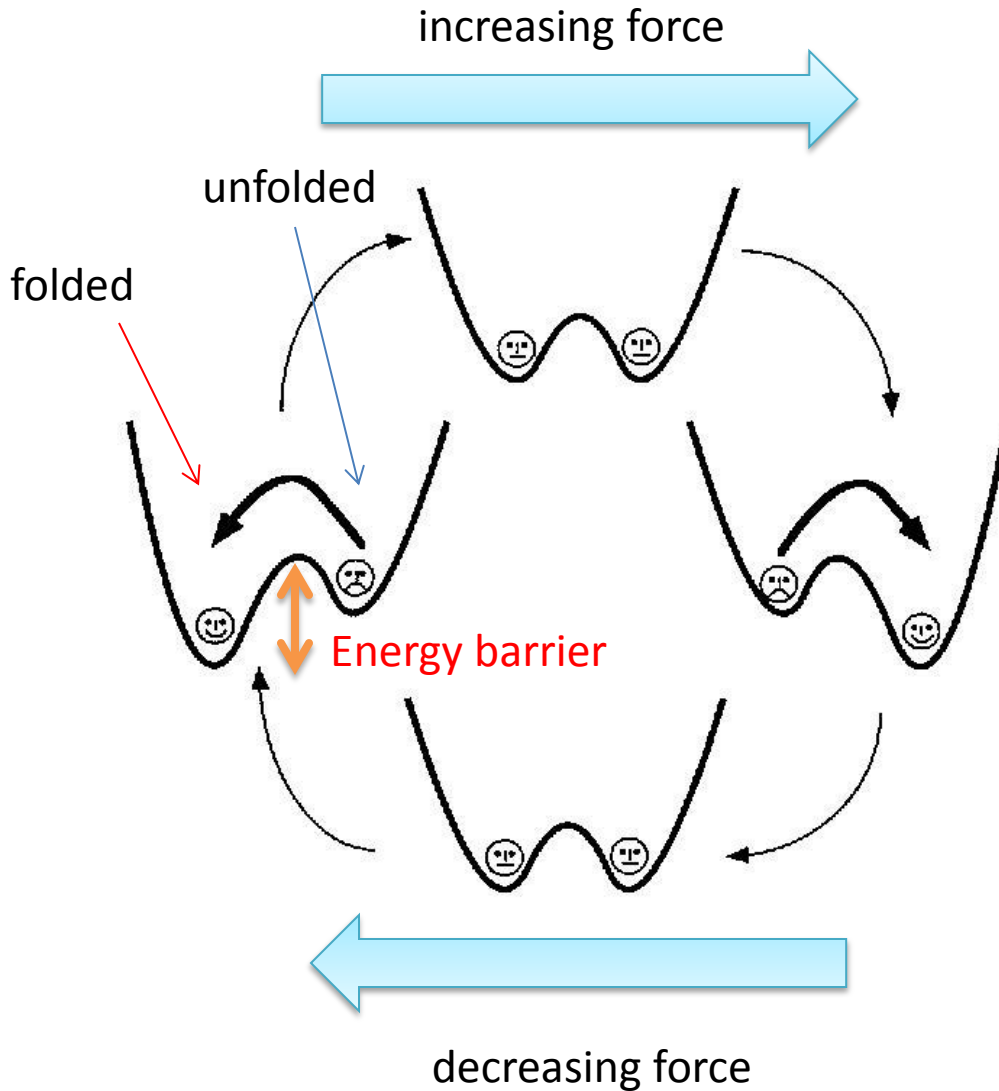


record the duration of time spent in a given state

histogram these values



RNA folding dwell times:



Recall, dwell time probability is:

$$P_{2 \rightarrow 1}(t) = k_+ e^{-k_+ t}$$

where,

$$k_+ = v \exp\left(-\frac{E_B - f\Delta z}{k_B T}\right)$$

applying the force lowers the barrier between the folded and unfolded state.

So in the optical tweezers experiment, they can measure the distribution and see the effect of force

Summary

The Boltzmann distribution gives us the ability to calculate the probability of observing a system at finite temperature in any particular microstate

This probability only depends on the energy (free energy) of the state

energy barrier affect the kinetics of reaction, not the final equilibrium

dwell times in a particular state depend on the barriers between the states

Optical tweezer experiments can measure directly the equilibrium likelihood and dwell times of each state.