I: Life and Energy

- May 21: Monday
- Lecture 1: What is life? An attempt at definition.
- Energy, heat, and work: Temperature and thermal equilibrium. The First Law. Thermodynamic states and state functions. Reversible and real processes. The Second Law and free energy. Why do living systems need energy? (B Lentz)
- May 23: Wednesday
- Lecture 2: Solutions and chemical potential; Osmotic pressure (B Lentz).
- **May 25: Friday**
- Lecture 3: Mother Nature plays dice: the Boltzmann distribution, partition functions and entropy. (B Lentz)

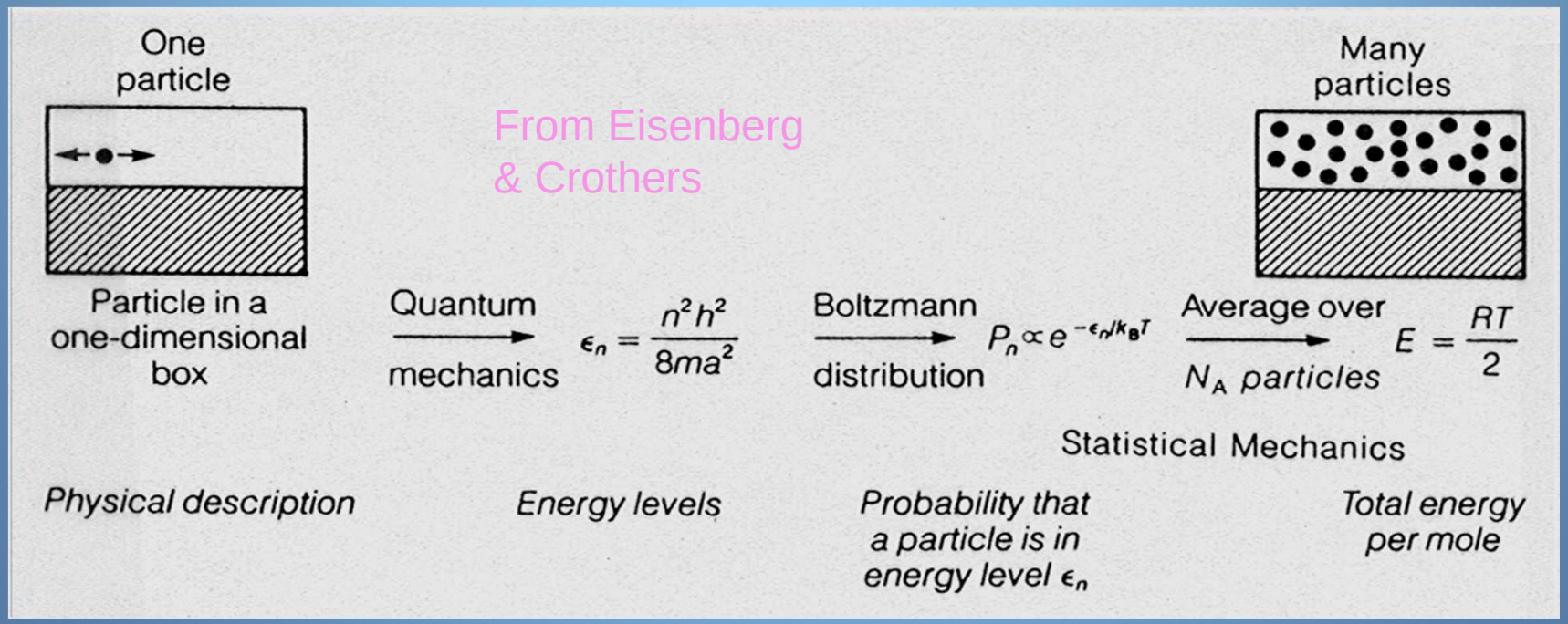
DO NOT STRESS THE MATH – PAY ATTENTION TO IDEAS!!!!

Thermodynamics: Average Properties of Large Numbers of Particles

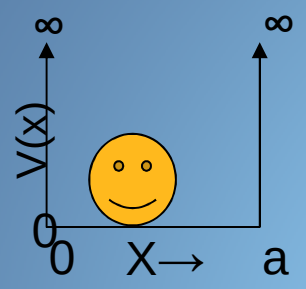
Biophysicists think about macromolecules with atomic structures. But we measure thermodynamic quantities that reflect average properties of molecules?

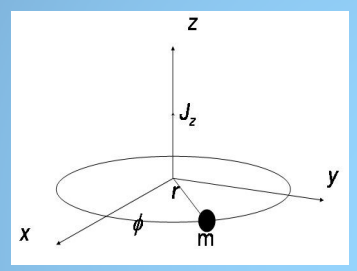
What do we mean when we talk about a protein "conformation"?

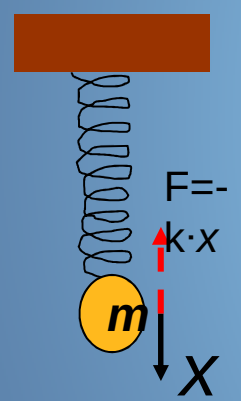
Statistical Mechanics is the path we take from a mechanical (quantum or classical) description of the energy and dynamics of individual molecules to a thermodynamic description of the behavior of large collections of molecules

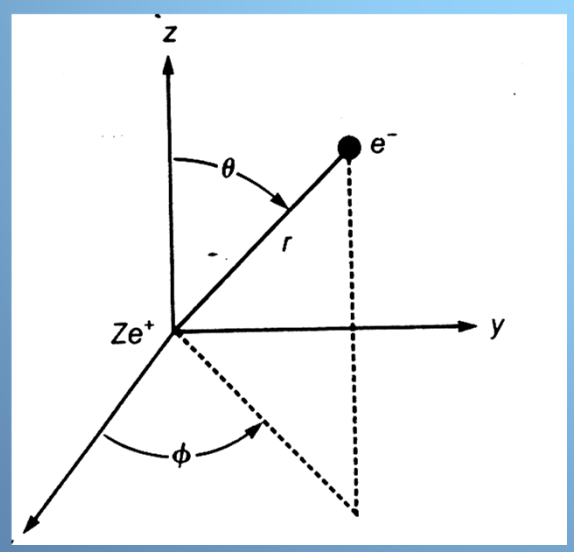


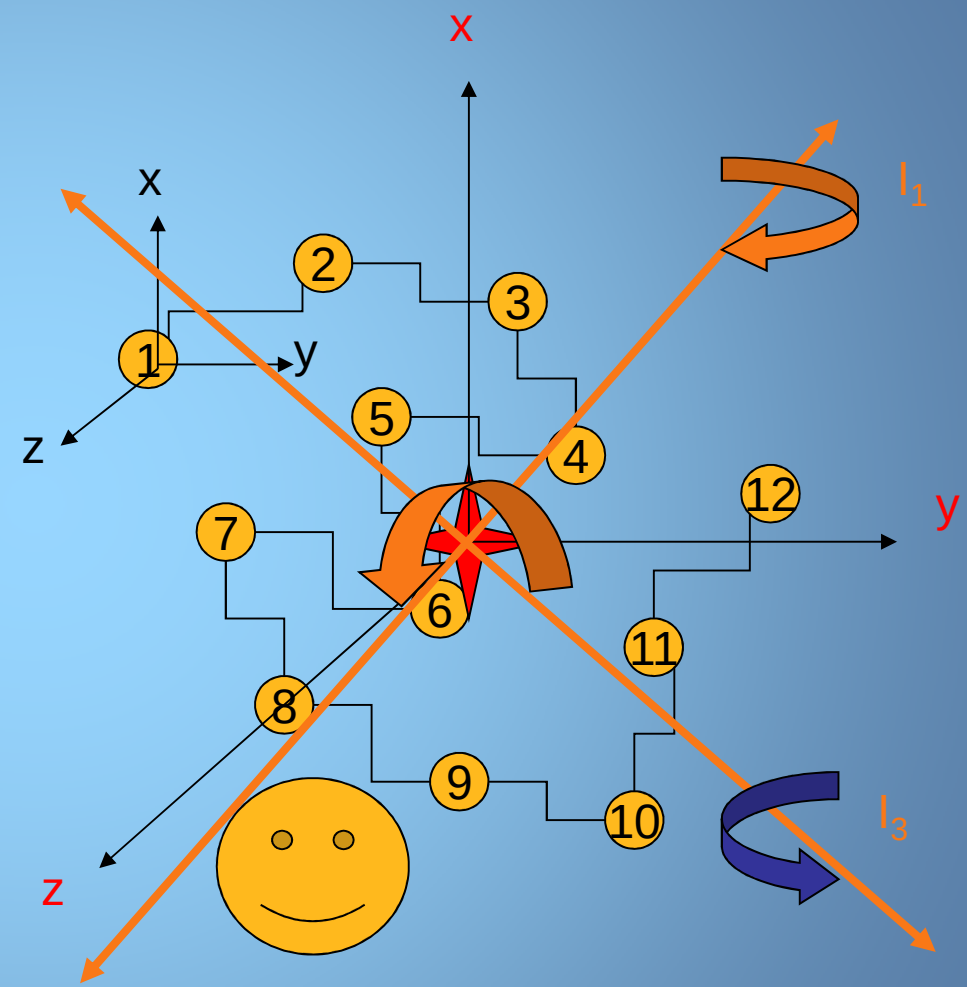
Simple Physical Models ⇨ Proteins











Ensembles

An Ensemble is a LARGE collection of N systems (mechanical or thermodynamic) whose properties are fixed by a common set of independent variable X,Y,Z but whose microscopic behavior differs between systems.

Look alike when observed from the outside

Different on the inside

$S_{1(X,Y,Z)}$	S_2	S_3	…
S_j	…		
S_m	…		
S_t	…		S_N

The Microcanonical Ensemble

We wish to describe the average state of a molecule with fixed energy (E/N) and having available to it a fixed volume (V/N). It can occupy quantum states $\Psi_1, \Psi_2, \Psi_3, \ldots$.

Absurd to consider the "thermodynamics" of one molecule! Why?

So consider a system with *N* INDEPENDENT molecules.

Consider an ensemble of systems, each with N such molecules, energy E, and volume V. In each element there are n_1 molecules in state Ψ_1, n_2 in state Ψ_2, *etc,* with the distribution of molecules over states being $\{n_i\}_j$ in the *jth element of the ensemble*. A Configuration.

N = # of elements

$N,V,E,\{n_i\}_1$	$N,V,E,\{n_i\}_2$	$N,V,E,\{n_i\}_3$	$\ldots$
$N,V,E,\{n_i\}_j$	$\ldots$		
$N,V,E,\{n_i\}_j$	$\ldots$		
$N,V,E,\{n_i\}_j$	$\ldots$		$N,V,E,\{n_i\}_j$

The Microcanonical Ensemble -2-

Each element in this ensemble has the same energy and volume but a unique microscopic description resulting from its particular distribution of distinct molecules over distinct quantum states.

Each ensemble element represents a unique quantum state of the system, but all with the same energy – MUCH DEGENERACY!

Here is where Mother Nature shoots Crap!

There are $\Omega(\{n_i\})$ elements having the distribution of molecules over quantum states designated as $\{n_i\}_j$. $\Omega(\{n_i\}_j)$ is the combinatorial factor for the number of ways to put N distinct balls into i distinct boxes with n_1 in box 1, n_2 in box 2, *etc. to produce* Ω_j *elements having the configuration* $\{n_i\}_j$.

$$\boxed{\Omega(\{n_i\}) = \binom{N}{n_1, n_2, \ldots n_i} = N! \prod_i \frac{g_i}{n_i}}$$

g_i is the degeneracy of the ith molecular quantum state

$$\sum_j \Omega(\{n_i\}_j) = N$$

Fundamental Postulates

We can obtain the average value of some mechanical system variable, *M*, in the system of interest if we make two assumptions:

The Basics Postulates of Statistical Mechanics

- All allowed distinct quantum states of a system are equally probable.

- Any system followed over time visits all quantum states with the same probability with which they occur in the ensemble: *Ergodic Condition*

Time-averaged properties equal ensemble-averaged properties as *t* and $N \rightarrow \infty$.

$$\text{where } \langle M \rangle_j = \frac{\sum_i n_{i,j} M_i}{\sum_i n_{i,j}} = \frac{\sum_i n_{i,j} M_i}{N}$$

$$\langle M \rangle = \frac{\sum_j \Omega(\{n_i\}_j) \langle M \rangle_j}{\sum_j \Omega(\{n_i\}_j)}$$

$$= \sum_j \Omega(\{n_i\}_j) \langle M \rangle_j \Big/ \mathfrak{N}$$

As N $\rightarrow \infty$, one term in this sum dominates. Our goal is to determine the distribution that corresponds to this maximum term.

The Most Probable Distribution Dominates

Boltzmann in Austria and Maxwell in England were concerned with the average properties of dilute gases in the mid 19th Century. Maxwell formulated his understanding in terms of random or stochastic motions of molecules and predicted Boyle's Law. Boltzmann used an ensemble or probabilistic approach and postulated that one distribution (*i.e.,* set $\{n_i\}_j$) would dominate and determine the properties if the number of molecules (N) was large.

Boltzmann set about finding the set $\{n_i\}_j$ that would maximize $\Omega(\{n_i\})$. At the same time, he had to insist that the system maintain its defining independent variable, in this case, N and E.

The problem is to maximize

$$\Omega(\{n_i\}) = N!\prod_i \frac{g_i}{n_i!}$$

Subject to the constrains that

$$E = \sum_i n_i \varepsilon_i; \quad N = \sum_i n_i$$

How to maximize the combinatorial distribution that involved factorials?

The Boltzmann Distribution

$$N! \approx N^N e^{-N} \sqrt{2\pi N}$$

$$\ln N! \approx N \ln N - N + \tfrac{1}{2}\ln(2\pi N)$$

Stirling's equation for *N*!

Maximize:

$$\ln \Omega(\{n_i\}) \approx N \ln N + \sum_i n_i (\ln g_i - \ln\ n_i) = -\sum_i P_i \ln\ P_i$$

Use the method of LaGrange to satisfy constraints.

$$B = N \ln N + \sum_i n_i \mathrm{l}\left(\ln g_i - \ln n_i\right) + \alpha\left(N - \sum_i n_i\right) + \beta\left(E - \sum_i n_i \varepsilon_i\right)$$

$$\frac{\partial B}{\partial n_i} = 0$$

α and β are Lagrange multipliers.

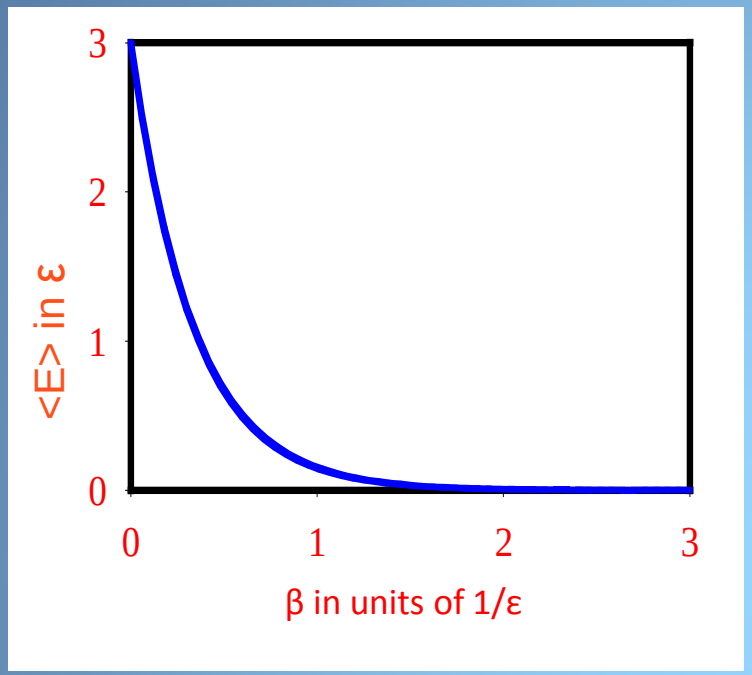
$$n_i = g_i \exp(-\alpha - \beta\varepsilon_i)$$

$$N = \sum_i n_i \Rightarrow n_i = N \frac{g_i \exp(-\beta\varepsilon_i)}{\sum_i g_i \exp(-\beta\varepsilon_i)}$$

$$P_i = \frac{n_i}{N} = \frac{g_i \exp(-\beta\varepsilon_i)}{\sum_i g_i \exp(-\beta\varepsilon_i)} = \frac{g_i \exp(-\beta\varepsilon_i)}{q}$$

P_i is the probability of molecules in the system being in the ith quantum state with energy ε_i. This probability is called the *Boltzmann distribution*.

The Meaning of β



To connect this probability distribution to thermodynamics, we must assign a value to β.

It is easy to show that the average energy of any system increases as $\beta \rightarrow 0$. The same thing occurs when $T \rightarrow \infty$.

Thus, Boltzmann chose $\beta = (1/k_B T)$, with the proportionality constant chosen to set the size of a degree of temperature and so as to give a rational definition to entropy.

$k_B = 1.99$ cal/mol/° K

$k_B T \simeq 600$ cal/mol at room to physiological temperature.

Note that α drops out from normalization. If we do not normalize, $\alpha = -\mu \cdot \beta$, where μ is the chemical potential of the molecule.

The Molecular Partition Function

The molecular partition function:

$$q = \sum_i g_i \exp(-\beta\varepsilon_i)$$

$$P_i = \frac{n_i}{N} = \frac{g_i \exp(-\beta\varepsilon_i)}{\sum_i g_i \exp(-\beta\varepsilon_i)} = \frac{g_i \exp(-\beta\varepsilon_i)}{q}$$

For simplicity, we assume g_i = 1 for all i.

q = sum of relative probabilities of each quantum state contributing to the average energy of the molecule. More states ⇒ larger q.

Connect partition function with thermodynamics:

$$\frac{\partial \ln q}{\partial \beta} = \frac{1}{q}\frac{\partial q}{\partial \beta} = \frac{-\sum_i \varepsilon_i \exp(-\beta\varepsilon_i)}{\sum_i \exp(-\beta\varepsilon_i)} = -\langle \varepsilon_i \rangle = -\frac{E}{N}$$

P_i

$$A = -N\, k_B T \ln q$$

$$E = -Nk_B \frac{\partial \ln q}{\partial (1/T)}$$

But Recall: $E = \dfrac{\partial (A/T)}{\partial (1/T)}$

Statistical Definition of Entropy

$$P_i = \frac{\exp(-\beta\varepsilon_i)}{\sum_i \exp(-\beta\varepsilon_i)} = \frac{\exp(-\beta\varepsilon_i)}{q}; \varepsilon_i = -\frac{1}{\beta}\ln(P_i q)$$

$$E/N = \frac{\sum_i \varepsilon_i \exp(-\beta\varepsilon_i)}{\sum_i \exp(-\beta\varepsilon_i)} = \sum_i \varepsilon_i P_i = \frac{1}{\beta}\sum_i (-\ln P_i - \ln q) P_i$$

$$E/N = -k_B T \sum_i P_i \ln P_i - k_B T \ln q \sum_i P_i$$

=S

$$\frac{E}{T} = -Nk_B \sum_i P_i \ln P_i - Nk_B \ln q = -Nk_B \sum_i P_i \ln P_i + \frac{A}{T}$$

$$S = -Nk_B \sum_i P_i \ln P_i = Nk_B \ln \Omega$$

Ludwig Edward Boltzmann; 1844-1906

This is Boltzmann's great achievement: a statistical interpretation of entropy!

Epitaph:

S = k ln W

Meaning of Partition Function

A Weighted Sum over All Quantum States Contributing to the Properties of the Molecule.

Internal Energy is a weighted sum over over the energies of all quantum states contributing to the properties of the system.

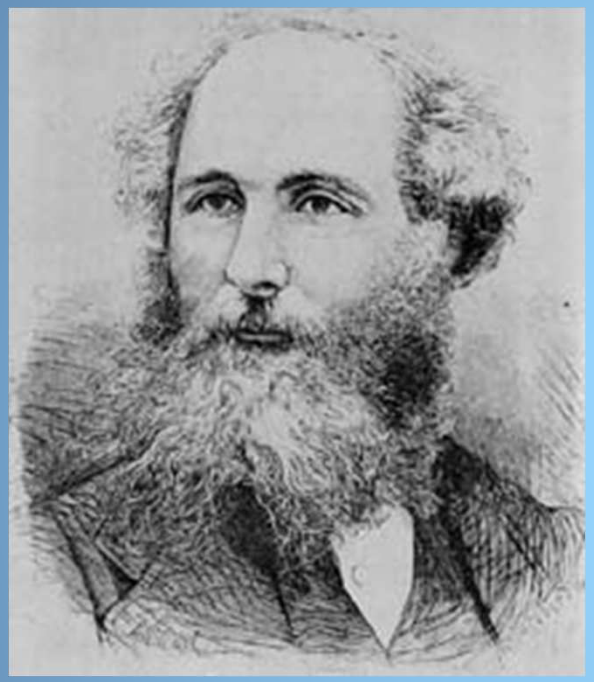
Two Parts: 1] From ground states: independent of T 2] From excited states: varies with T ("thermal")

Entropy is a sum over the log of the probabilities of occupancy of each of the quantum states contributing to the system. TS is that portion of the internal energy required to maintain the maximal distribution over quantum states.

Free energy is that portion of the internal energy available to do work while S is maintained or increased.

Let's Not Forget Maxwell

James Clark Maxwell, 1831-1879



Maxwell's daemon can make a cold molecule give up heat, but only during a brief window of time.

His skepticism about Boltmann's postulate ➪ key link between stochastic and thermodynamic gas theories: Events that violate the second law of thermo on a macroscopic scale are still kinetically possible on a molecular scale, but not likely.

Best known for his equations describing the behavior of an electromagnetic field. ➪ EM waves travel at the speed of light.

Developed a kinetic theory of gases 17 years before Boltzmann developed his statistical theory of gases.

Now Let's Build a Protein!

Recall that we showed that the mechanics of a macromolecule could be described first by separating the motions of electrons and nuclei (Born Approximation) and then by separating the nuclear motions into independent motions: 3 translations of the center of mass, 3 rotations about principle axes, and 3N-6 internal harmonic oscillations.

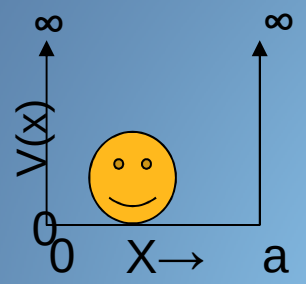
The total energy of the macromolecule is then the sum of the energies associated with electronic and 3N independent nuclear quantum states:

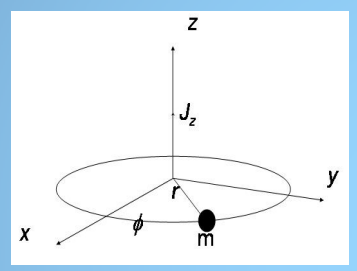
$$\varepsilon_{i,j,k,l} = \varepsilon_{\text{elec},i} + \varepsilon_{\text{trans},j} + \varepsilon_{\text{rot},l} + \varepsilon_{\text{vib},k}$$

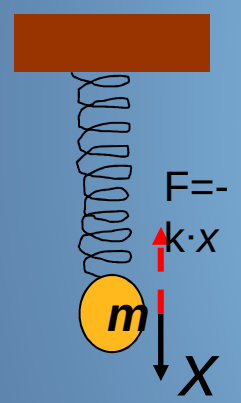
Properties of exponential function ➪ *sum of exponentials of a sum of independent terms = product over sums of exponential for each term* – key thing is that the indices are independent.

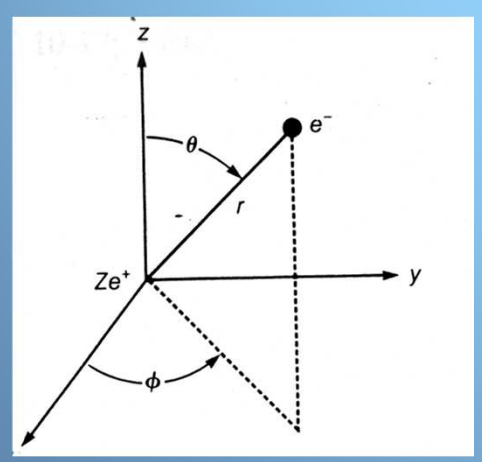
$$q = \sum_{i,j,k,l} e^{-\left(\varepsilon_{\text{elec},i}+\varepsilon_{\text{trans},j}+\varepsilon_{\text{rot},l}+\varepsilon_{\text{vib},k}\right)/k_B T} = \left(\sum_i e^{-\varepsilon_{\text{elec},i}/k_B T}\right)\left(\sum_j e^{-\varepsilon_{\text{trans},j}/k_B T}\right)\left(\sum_l e^{-\varepsilon_{\text{rot},l}/k_B T}\right)\left(\sum_k e^{-\varepsilon_{\text{vib},k}/k_B T}\right)$$

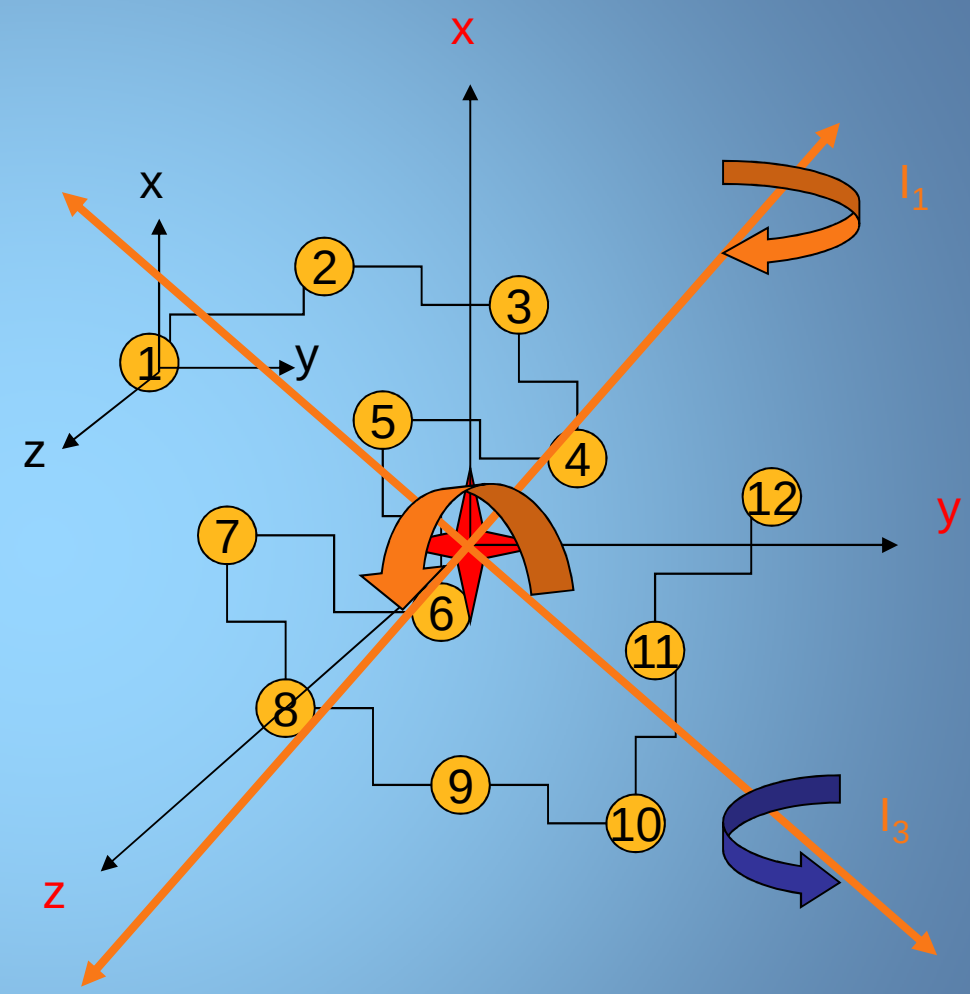
Simple Physical Models ⇨ Proteins











Excluding the electrons, how many *motional degrees of freedom* does this protein have?

3 translations, 3 rotations, how many vibrations?

Voila!!

$$q = q_{elec} q_{trans} q_{rot} q_{vib}$$

We have broken down the daunting problem of describing the average mechanical behavior of a macromolecule to that of describing the quantum behavior of its electronic distribution (LCAO-MO or other approximate methods solve this) plus the average behavior of a particle in a box, a rigid rotator, and a set of independent harmonic oscillators!

We describe in extra slides at the end of this lecture the partition function of each of these.

Fundamental Properties of Each Partition Function.

The free energy (enthalpy and entropy) of a protein can be described in terms of the kinetic and potential energy of all these motions!

Protein “conformation” defined.

Translational Partition Function

Energy levels for a particle in a 1-D box:

$$E_n = \frac{n^2 h^2}{8ma^2}, \quad n = 1,2,3,\ldots$$

$$q_{trans,x} = \sum_n \exp\left(-\frac{n^2 h^2}{8ma^2} / k_B T\right)$$

Because exp-(E_n/k_BT) always <<<1⇒

$$q \approx \int_0^\infty dn \exp\left(-\frac{n^2 h^2}{8ma^2 k_B T}\right) = \frac{1}{2}\left(\frac{8ma^2 k_B T \pi}{h^2}\right)^{\frac{1}{2}} = \frac{a}{\Lambda}; \quad \Lambda = \left(\frac{h^2}{2\pi m k_B T}\right)^{\frac{1}{2}} = \text{deBroglie wavelength}$$

$$q_{\text{trans}} = q_{\text{trans},x}\, q_{\text{trans},y}\, q_{\text{trans},z} = \frac{abc}{\Lambda^3} \quad \Rightarrow \quad \boxed{q_{trans} = \frac{V}{\Lambda^3}}$$

$$A_{\text{trans}} = -k_B T \ln q_{\text{trans}} = -k_B T \ln V + 3k_B T \ln \Lambda$$

$$P = -\left(\frac{\partial A}{\partial V}\right)_{N,T} = \frac{k_B T}{V}$$

Ideal Gas Law

The Big Four

$$q_{elec} = g_0 e^{-\beta\varepsilon_0}$$

Only one term: $\varepsilon_1 - \varepsilon_0 >>> k_B T$

$$q_{trans} = V / \Lambda^3$$

De Broglie Wavelength = λ= *h*/*p*

Thermal De Broglie Waveleenght = Λ

$$\Lambda = \left(h^2 / 2\pi m k_B T \right)^{1/2}$$

$$A_{trans} = -k_B T \ln q_{trans} = -k_B T \ln V + 3 k_B T \ln \Lambda$$

$$P = -\left(\frac{\partial A}{\partial V} \right)_{N,T} = \frac{k_B T}{V}$$

Boyle's Law

$$q_{1,2,3}^{rot} = \frac{\sqrt{\pi}}{\sigma} \left(\frac{T^3}{\Theta_1^{rot} \Theta_2^{rot} \Theta_3^{rot}} \right)$$

Rotational Temperature

$$\Theta_i = \hbar^2 / 2 k_B I_i$$

$$q_{\mathrm{vib},i} = \sum_{n=0} \exp[-\frac{(n+\frac{1}{2})h\nu_i}{k_B T}] = \frac{\exp(-h\nu_i / 2k_B T)}{1 - \exp(-h\nu_i / k_B T)}$$

Any spring, *i.e.*, all vibrational frequencies.

$$q_{\mathrm{vib},i} \approx \int_0^\infty dn \exp[-\frac{nh\nu_i}{k_B T}] = \frac{k_B T}{h\nu_i}$$

Weak springs, , *i.e.*, $h\nu << k_B T$

Equipartition of Energy

Recall that when we made the connection between the partition function and thermodynamics, we noted that:

$$E = -Nk_B \frac{\partial \ln q}{\partial (1/T)}$$

$$E_{trans} = -k_B \frac{\partial(\ln V - \ln \Lambda^3)}{\partial(1/T)} = 3k_B \frac{\partial \ln \Lambda}{\partial(1/T)} = 3k_B \frac{\partial\left(\frac{1}{2}\ln\frac{1}{T}\right)}{\partial(1/T)} = \frac{3k_B T}{2}$$

This holds because the energy levels of the particle in a box are very closely spaced, *i.e.*, it holds in the *classical limit* in which all quantum states are occupied with high probability. It also holds for vibration and rotation whenever ΔE (between states)<<$k_B T$.

The general result is called the thermal energy *Equipartition Theorem*: $k_B T/2$ per degree of freedom in kinetic and potential energy.

Rotational Partition Function

$$E^1_{rot} = m^2 k_B \Theta^1_{rot}; \quad m = 0, \pm 1, \pm 2, \ldots; \quad \Theta^1_{rot} = \frac{h^2}{8\pi^2 I_1 k_B}$$

$$q^1_{rot} = \sum_{m=-\infty}^{\infty} \exp\left(-{m^2 \Theta^1_{rot}}/{T}\right) = \pi^{1/2}\left(\frac{T}{\Theta^1_{rot}}\right)^{1/2}$$

$$q^{rot}_{1,2,3} = \frac{\sqrt{\pi}}{\sigma}\left(\frac{T^3}{\Theta^{rot}_1 \Theta^{rot}_2 \Theta^{rot}_3}\right)$$

Divide by πσ because of degeneracy of rotations about 3 axes.

$$E^1_{rot} = -k_B \frac{\partial\left(\ln \pi^{1/2}\left(\frac{T}{\Theta^1_{rot}}\right)^{1/2}\right)}{\partial(1/T)} = k_B \frac{\partial \ln T^{1/2}}{\partial(1/T)} = \frac{k_B T}{2}$$

In the absence of a potential energy contribution, the *Equipartition Theorem* again gives ½k_BT per kinetic energy degree of freedom.

Vibrational Partition Function

Harmonic potential ⇒ $E_{n,i} = (n+1/2)v\beta_i$

$$q_{vib} = \prod_{i=1}^{3N-6} q_{vib,i}$$

$$q_{\mathrm{vib},i} = \sum_{n=0} \exp[-\frac{(n+\frac{1}{2})h\nu_i}{k_B T}] = \frac{\exp(-h\nu_i / 2k_B T)}{1-\exp(-h\nu_i / k_B T)}$$

When $k_B T \gg h\nu$ (in the so-called *classical limit*) ➪

$$q_{\mathrm{vib},i} \approx \int_0^\infty dn \exp[-\frac{nh\nu_i}{k_B T}] = \frac{k_B T}{h\nu_i}$$

Note $h \simeq 2.86$ cal·mol^{-1}·cm so many vibrations are not in the classical limit.

$$E_{vib,i}^{classical} = -k_B \frac{\partial \ln q_{vib,i}}{\partial(1/T)} = -k_B \frac{\partial \ln T}{\partial(1/T)} = -k_B T$$

In the Equipartition Theorem limit, we see ½k_BT from each kinetic energy and each potential energy degree of freedom.

Tight Springs

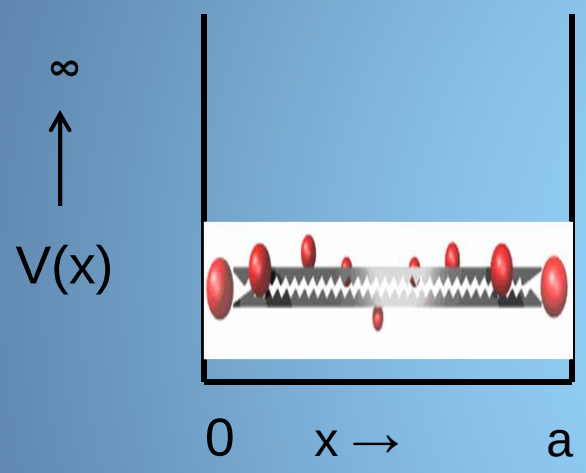
When hv >> k_BT, we are far from the classical limit, and the partition function for motion in a potential is more complicated.

$$q_{vib} = \sum_{n=0}^{\infty} \exp\left(-\frac{(n + 1/2)h\nu}{k_B T} \right) = \frac{\exp(-h\nu / 2k_B T)}{1 - \exp(-h\nu / k_B T)} \neq \frac{k_B T}{h\nu}$$

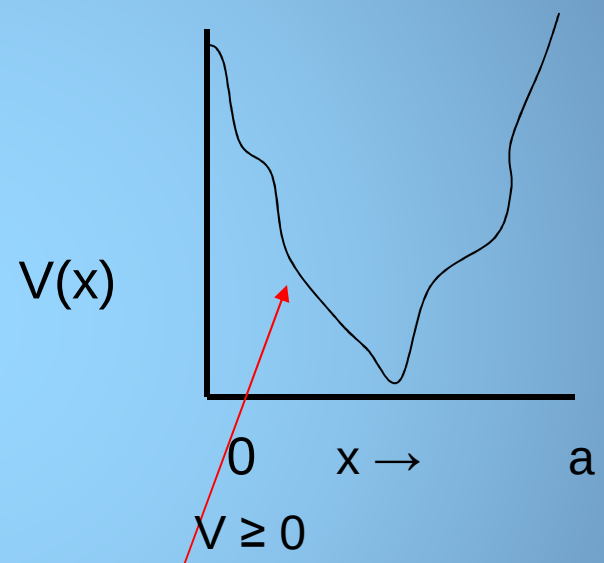
In general, for hv < ~ 10% k_BT, we can use the classical approach.

Hindered Translation & Rotation

What is hindered motion?



V = 0,∞



$$\underline{\underline{H}} = \frac{m}{2}\frac{\partial^2}{\partial \underline{r}^2} + V(\underline{r})$$

Requires different treatment and different equipartition theorem.

Electronic Molecular Partition Function

$$E_n = -\frac{1}{n^2}\frac{e^2}{2a_0},\ n = 1, 2, 3, \ldots$$

$$E_2 - E_1 = \frac{3e^2}{8a_0} = \frac{3 \times 332 \dfrac{kcal/mol}{e^2/\mathring{A}}}{8 \times 0.529\,\mathring{A}} \approx 200 \text{ kcal/mol} \square\ k_B T$$

Only the ground state is occupied at room temperature.

$$q_{elec} = \sum_n \omega_n \exp - \left(-\frac{1}{n^2}\frac{e^2}{2a_0} \Big/ k_B T \right) \square\ \omega_0 \exp\left(\varepsilon_{elec}^0 \Big/ k_B T \right)$$

$$A_{elec} = -k_B T \ln \omega_0 + \varepsilon_{elec}^0;\quad E_{elec} = \varepsilon_{elec}^0$$

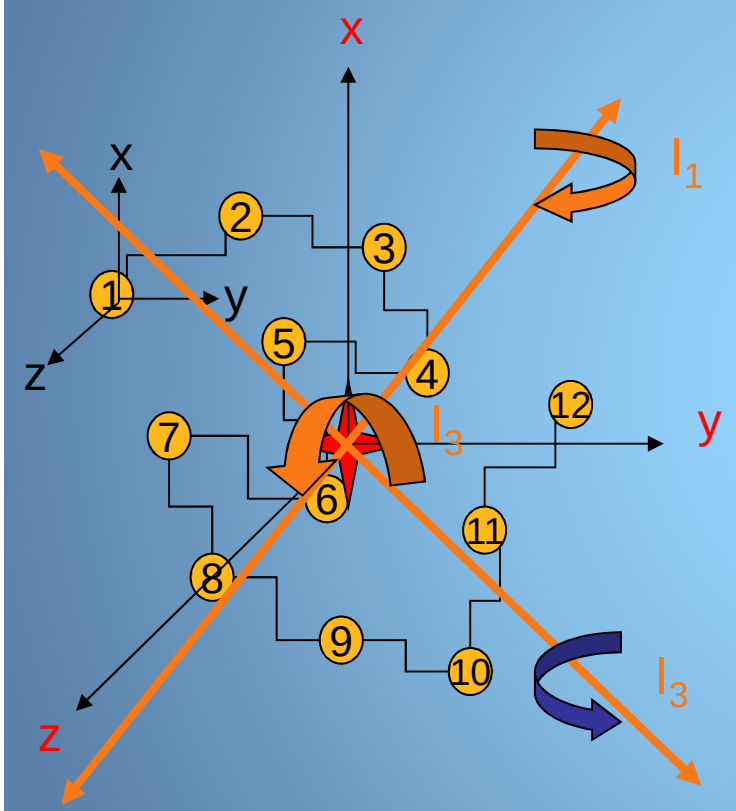
Protein Molecular Partition Function

$$q = q_{elec} q_{trans} q_{rot} q_{vib}$$

We have described the average mechanical behavior of a rigid body macromolecule in terms of the quantum behavior of its electronic distribution (LCAO-MO or other approximate methods solve this) plus the average behavior of a particle in a box, a rigid rotator, and a set of independent harmonic oscillators.

Unfortunately, proteins are not generally rigid bodies!

What Does This Have to Do with Macromolecules?



We have treated our protein as a rigid body. But ∃ only one global arrangement of particle or atoms in a rigid body. Not true for proteins!

Rotations about bonds (not included in rigid body treatment) ⇨ multiple global arrangements called protein "conformations".

Protein Conformational States

$q_{1=}$ $q_e q_{trans} q_{rot} q_{vib}$ ↔

q_2 ↔

q_3 ↔

q_4

Which one is most likely?

But what if $q_1 \sim q_2 \sim q_3 \sim q_4$?

Largest q!

Multiple Minima Problem

Multiple conformation states of locally minimum free energy!

Number of minima = $O(p^{\text{number of peptide bonds}})$ (p>1)

Each conformation must contribute to the partition function.

Recall molecular partition function is sum over all possible quantum sates of the molecule.

$$q = \sum_j q_j$$

Protein Partition Function

A protein exists in a multitude or "ensemble" of possible rigid body conformations, such that there are n_1 of structure *1*, n_2 of structure *2*,…, n_j of structure *j*,…. In a collection of N proteins, how many are in the jth conformation?

Assume protein configurations do not interact – i.e. and ideal mixture at N,T,V.

$$\Theta = \frac{N!}{\prod_j n_j!} \prod_j q_j$$

Canonical Partition Function

But how many copies of the jth microstructure (*i.e.*, j^{th} rigid body structure) are present? We do not know $\{n_j\}$!

We must find the distribution $\{n_j\}$ that maximizes the number of ways of distributing proteins over their microstates!

This is something like the problem we faced of finding the distribution of molecular quantum states that maximized the microcanonical or molecular partition function.

To do this we need a new type of partition function that does not fix $\{n_j\}$, *i.e.*, one in which each element of the corresponding ensemble does not have its composition fixed. This is called a *Grand Canonical Ensemble and Partition Function*.

The Statistical Nature of a Protein

The probability of observing any conformation ($P_j = n_j/N$) must be related to the value of its molecular partition function, which would be $P_j = q_j/Q$ if {nj} were fixed. But we must find the set $\{n_j\}$ that maximizes the entropy of mixing different microstructural states at the same time that it allows for the probability of observing each microstate being described by the Boltzmann distribution. The grand canonical partition function (Ξ) does this for us.

$$\Xi = q^N = \left(\sum_j q_j\right)^{\sum_j n_j} = \sum_{\{n_j\}} \frac{N!}{\prod_j n_j!} \prod_j (q_j)^{n_j}$$

$$N = \sum_j n_j; E = \sum_j n_j E_j; V; \{\mu_j\}$$

To simplify a slightly complex treatment, we get the the probability of observing each microstate is related to its chemical potential, μ_j.

$$n_i = P_i N = \frac{e^{-\mu_i^o / k_B T}}{\sum_j e^{-\mu_j^o / k_B T}} = \frac{e^{-\mu_i^o / k_B T}}{\Phi}$$

Φ is termed the molecular grand partition function.

$$q_j = e^{-\beta \mu_j}$$

Statistical Weight of microstate *j*.

Study Questions

You should be able to answer easily the following questions. If you can't, please go over these with you Study Group or TA to be sure that you understand how to answer them.

1. From the perspective of Boltzmann, what is entropy?

2. From the Ideal Mixture Law, is there any solute that is completely insoluble in any solvent? Explain or give example.

3. Binding of a ligand to a protein involves moving it from a very large box (the solution) to a very small one (the binding site). If we assume that only the translational term of the ligand molecular partition function changes during this process, is this a favorable process? Explain. So, what causes a ligand to bind?

4. A protein has 100 atoms. If all of its internal vibrations have frequencies < 30 cm^{-1} (a very weak vibration), what is its thermal energy? Explain.

5. A particular protein P is known to have 4 conformations for which $q_1 > q_2 > q_3 >> q_4$. Its distribution over conformational states is described by $\{n_i\}$. Which conformation is most likely? Will this conformation dominate the thermodynamic properties of the protein? Why or why not? Conformation 4 is known to bind ligand L. Will the complex PL every be observed? Why or why not?

Useful (?) Extra Slides

1. Partition functions for independent motions

2. Useful Applications

3. Other partition functions correspond to different choices of independent variables: e.g. Canonical Partition Function (T,V,N)

4. Independent and Distinguishable Molecules

5. Ideal Mixture: Independent Molecules

6. Very tough physics: non-independent particles

Useful Applications

- We could not cover in class some useful applications of Statistical Thermodynamics
- The following slides address:

1] the result of changing variable to the more useful set T, V, N: Canonical Partition Function; identical and distinguishable particles.

2] the nature of the unitary chemical potential for an ideal mixture/solution.

3] Complications faced with interacting particles.

4] The statistical nature of protein conformation.

1] Change Independent Variables

Molecular Partition Function: Molecule with energy E in a volume V. We derived this for a set of N identical and independent molecules.

We most often have a collection of N molecules (closed system) in a volume V at temperature T (*i.e,* thermal equilibrium). So we must change independent variables ⇨ new Partition Function!

The Canonical Partition Function

Canonical Ensemble: each element is a *thermodynamic* system with fixed T, N, and V but different energy E_k. All elements in thermal equilibrium. As for the microcanonical ensemble, all elements are independent.

We make no assumption about the distribution of molecules between their quantum states or about interactions between molecules.

N, V, T E_1	N, V, T E_2	N, V, T E_3	…
N, V, T E_k	…		
N, V, T E_m	…		
N, V, T E_p	…		N, V, T $E_{\mathfrak{N}}$

The Canonical Boltzmann Distribution in E_i

What is the most probable configuration consistent with the constraint that the thermodynamic energy (*i.e.*, the average energy <E>) is fixed?

Just as we did for the microcanonical partition function, we maximize $\Omega(\{m_j\})$ with respect to $\{m_j\}$ subject to $\Sigma_k = \mathcal{N}$ (the total number of elements, $\rightarrow\infty$) and $\Sigma_k E_k = \mathcal{N}\langle E\rangle$ (the total energy of the ensemble).

$$P_j = \frac{\exp(-\frac{E_j}{k_B T})}{Q}; \quad where \quad Q = \sum_i \exp(-\frac{E_j}{k_B T})$$

$$A - A(0) = -k_B T \ln Q$$

$$U - U(0) = \langle E \rangle = \frac{\partial(A/T)}{\partial(1/T)} = -\frac{\partial \ln Q}{\partial(1/k_B T)}$$

$$S - S(0) = -\frac{\partial A}{\partial T} = -k_B \ln \Omega$$

We make the same identifications with thermodynamic functions.

Special Case: Independent Molecules

$$\boxed{Q = \sum_{k=1}^{\aleph} \exp\left\{-\left(E_k / k_B T\right)\right\}}$$

$$= \sum_{k=1}^{\aleph} \exp\left\{-\frac{\sum_i n_{i,k}\varepsilon_{i,k}}{k_B T}\right\} = \sum_{k=1}^{\aleph} \exp\left\{-\frac{\sum_{l=1}^{N} \varepsilon_{l,k}}{k_B T}\right\}$$

1] The energy E_k of an ensemble element comes about by summing over the molecular quantum states (index *i*) of the *N* molecules in the kth element, where $\{n_i\}_k$ is distribution of molecules over molecular quantum states. This sum can also be written as the sum over all molecules (index *i*).

2] For $\aleph \rightarrow \infty$, all possible quantum states are represented, and we assume we can replace the infinite sum over *k* by an infinite sum over quantum states *i*. At the same time, replace exponential of sum by product of exponentials.

$$Q = \sum_{i=1}^{\infty} \prod_{l=1}^{N} \exp\left\{-\frac{\varepsilon_{l,i}}{k_B T}\right\}$$

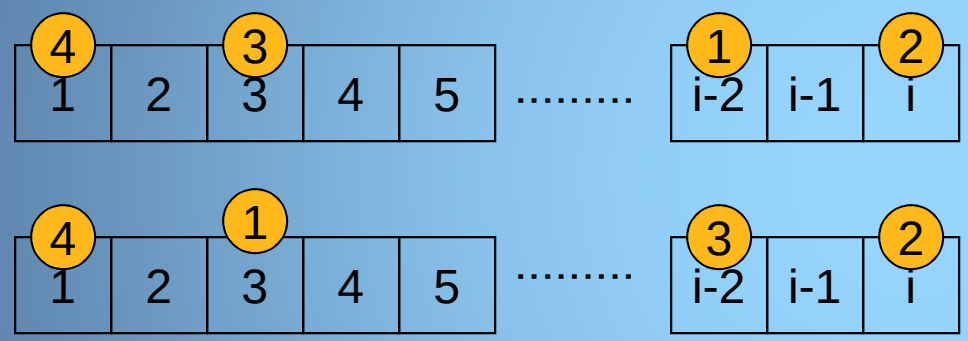
3] Therefore, we have a *sum of products of exponentials of independent terms.* We know that this is *the product over sums of exponential for each term.*

$$\boxed{Q = \prod_{l=1}^{N} \sum_{i=1}^{\infty} \exp\left\{\frac{\varepsilon_{l,i}}{k_B T}\right\} = \prod_{l=1}^{N} q_l}$$

Distinguishable *versus* Indistinguishable Molecules

Derivation of *Q* for independent molecules assumed that all molecules are distinct (*distinguishable*).

If the molecules are *indistinguishable*, we have over-counted the number of configurations of the system in obtaining the partition function.



These two configurations are physically the same if the molecules (numbered balls) are indistinguishable.

When the number of states >> the number of molecules (*i.e.*, < one molecule/state; *classical statistics*), we can correct by the dividing by the number of ways of assigning *N* molecules to *N* distinguishable states:

$$Q = \frac{q^N}{N!}$$

For different types of molecules: $Q = \frac{q_A^{N_A}}{N_A!}\frac{q_B^{N_B}}{N_B!}\cdots\frac{q_X^{N_X}}{N_X!}$

1] A Fully Describable System: Ideal Mixture

In developing Molecular Partition Function, assumed independence. ∴ Individual molecules are easily described!

The challenge in describing any system: counting configurations!

When molecules interact, each arrangement of molecules has a different energy, so some configurations are counted more heavily than others.

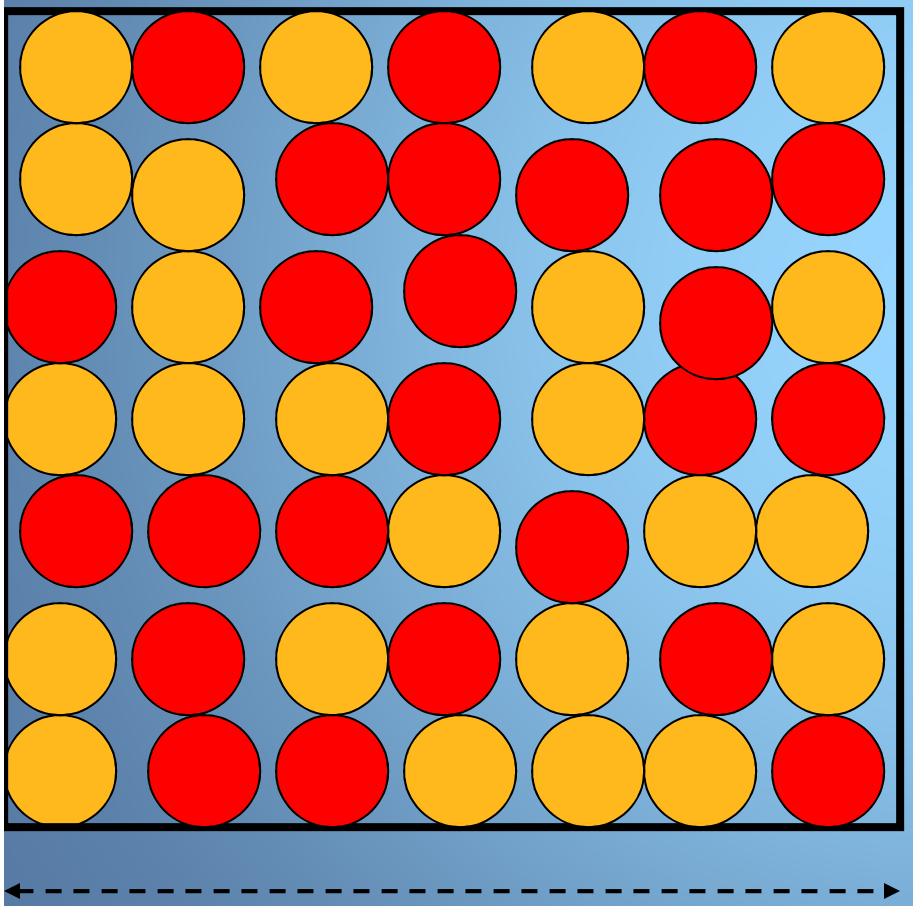
Simplifying Approximations: 1] Molecules do not interact.

2] Molecules all of same size. ⇨ Ideal Mixture.

Not a great approximation, but OK for fairly dilute solutions.

Ideal Mixture – 2 -

$$Q = \frac{q_A^{N_A}}{N_A!}\frac{q_B^{N_B}}{N_B!} = \frac{\left(q_{A,elec}q_{A,vib}q_{A,rot}q_{A,trans}\right)^{N_A}}{N_A!}\frac{\left(q_{B,elec}q_{B,vib}q_{B,rot}q_{B,trans}\right)^{N_B}}{N_B!}$$



Only q_{trans} depends on V; all other terms are intensive. Separate terms:

$$Q = q_{A,\text{int}}^{N_A}\frac{\left(q_{A,trans}\right)^{N_A}}{N_A!}q_{B,\text{int}}^{N_B}\frac{\left(q_{B,trans}\right)^{N_B}}{N_B!}$$

$$q_{A,\text{int}} = q_{A,elec}q_{A,vib}q_{A,rot};\ q_{B,\text{int}} = q_{B,elec}q_{B,vib}q_{B,rot}$$

$$Q \square\ q_{A,\text{int}}^{N_A}\left(\frac{eq_{A,trans}}{N_A}\right)^{N_A} q_{B,\text{int}}^{N_B}\left(\frac{eq_{B,trans}}{N_B}\right)^{N_B}$$

$$A = -k_BT\ln Q =$$

$$-k_BTN_A\ln q_{A,\text{int}} - k_BTN_A(\ln V - \ln\Lambda^3 - \ln N_A + 1)$$

$$-k_BTN_B\ln q_{B,\text{int}} - k_BTN_B(\ln V - \ln\Lambda^3 - \ln N_B + 1)$$

Ideal Mixture -3-

$$A = -k_B T \ln Q =$$

$$-k_B T N_A \left(\ln q_{A,\text{int}} - \ln \Lambda^3 + 1\right) + k_B T N_A (\ln {N_A}/{V})$$

$$-k_B T N_B \left(\ln q_{B,\text{int}} - \ln \Lambda^3 + 1\right) + k_B T N_B (\ln {N_B}/{V})$$

$$\ln {N_B}/{V} = \ln {N_B}/{\nu(N_A + N_B)} = \ln X_B - \ln \nu$$

$$\text{So, } A = N_A \mu_A^0 + k_B T N_A \ln X_A + N_B \mu_B^0 + k_B T N_B \ln X_B$$

v = volume per mol of A = volume per mol of B

From this, you can derive the Ideal Mixture Law:

$$\mu_A = \mu_A^0 + k_B T \ln X_A; \quad \mu_B = \mu_B^0 + k_B T \ln X_B$$

This is the familiar state equation for an ideal mixture/ solution. This gives meaning to the quantities μ_A^0 and μ_B^0. For an ideal mixture, μ^0 reflects the behavior of pure A. For ideal solution, it reflects A surrounded by solvent.

$$\mu_A^0 = -k_B T \ell n \left(\frac{e \cdot \upsilon \cdot q_{A.\text{int}}}{\Lambda_A^3} \right)$$

3] Non-Independent Particles!

$$Q = \sum_{j=1}^{\mathfrak{M}} \exp\left\{-\left(E_j / k_B T\right)\right\}$$

Derivation of Q did not require the assumption of independence. Q can still be defined for non-independent (*i.e.*, correlated or interacting) particles.

Long range correlations ⇨ Ψ_j involves many or all particles.

E_j may be very widely spaced ⇨ $Q \rightarrow \exp\{E_1/k_B T\}$

E_j may be very closely spaced ⇨ $Q >$ or $< Q_{independent}$

Very short range correlations ⇨ local $\Psi_j = \Psi_a \Psi_b \Psi_c \cdots$, where each Ψ_i involves only local groups of particles.

Key Problem: Counting configurations depends on all particles, which determine Ψ_k and E_k.

Whatever be the case, if we can find some way to count quantum states and weight them by the Boltzmann probability ⇨ Q