Announcements:

1. "advanced copy" of today's notes in Files → Week 1 folder on Canvas

   (will fill in a bit as we go)

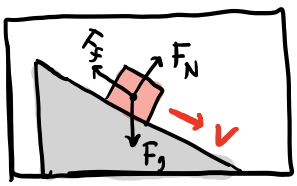
2. First feedback assignment posted (due Sat)

3. Optional practice problem posted

   (Files → Week 1 folder on Canvas)

Lecture 2: Introduction/Review of Statistical Mechanics

* Stat mech = set of tools to:



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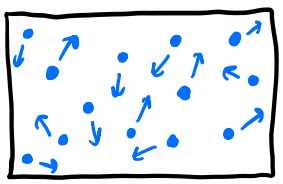
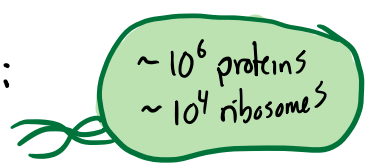


① predict behavior of systems w/ too many parts to predict individually

② understand causes & consequences of "thermal noise"

⇒ why relevant for biophysics?

① single cells contain large # molecules:



② thermal noise is important for design & function of many cellular processes

⇒ statmech is usually subject of whole course

⇒ will give abbreviated intro / review today

(focusing on parts we'll need for this course)

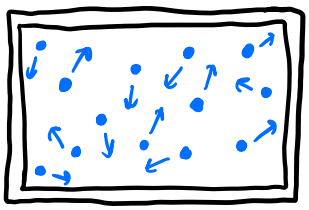
For longer intro to stat mech in biology,
see Chapters 5+6 of Physical Biology of the Cell

Plan: today = basic framework

next time = bio applications

Fundamental Principle of Stat Mech:

In a closed system at equilibrium



$\Rightarrow$ all allowed states of system occur w/ equal probability → "microstates"

$$P_s = \text{probability of observing system in microstate } s = \frac{1}{\Omega}$$

$\Omega \leftarrow$ total # of microstates

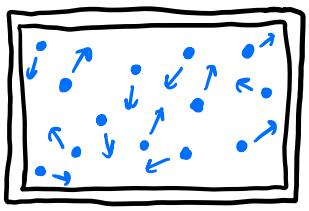
$\Rightarrow$ Why is this true?!?

$\Rightarrow$ Deep question! (tricky to prove in general...)

$\Rightarrow$ Here, will treat as assumption

$\Rightarrow$ Key Question: What is a microstate?
& how do we count them?

Example: "Ideal Gas" = "collection of barely interacting, indistinguishable particles"



⇒ N particles of mass m

⇒ confined to box of size V

⇒ each particle has position $\vec{x}_i = (x_i, y_i, z_i)$

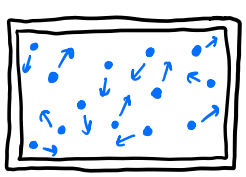
& momentum $\vec{p}_i = (p_x, p_y, p_z) = (mv_x, mv_y, mv_z)$

⇒ Microstate, $s = (\vec{x}_1, \vec{p}_1, \vec{x}_2, \vec{p}_2, \ldots, \vec{x}_N, \vec{p}_N)$ ⇒ 6N total variables

⇒ which microstates are allowed?

① $N = \text{const}$

② $\vec{x}_i \in V = \text{const}$



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③ Physics: total energy $E = \sum_{i=1}^{N} \frac{|\vec{p}_i|^2}{2m} = \text{const}$

Counting microstates: total # of microstates, $\Omega(N,V,E)$

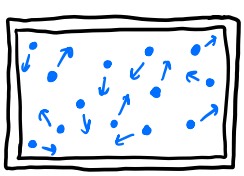
$$\Omega = \frac{1}{N!} \overbrace{\sum_{\vec{x}_1} \sum_{\vec{p}_1} \cdots \sum_{\vec{x}_N} \sum_{\vec{p}_N}}^{\text{sum over microstates}} 1^{\times} \left\{ \begin{array}{l} \vec{x}_i \in V \\ \sum_i \frac{|\vec{p}_i|^2}{2m} = E \end{array} \right\}$$

allowed microstates

$\frac{1}{N!}$ → particles are indistinguishable (from QM)

$\Rightarrow$ this is a sum we can solve! (see supplemental notes)

$$\log \Omega(N,V,E) \approx N \log\left[\frac{V}{N}\left(\frac{E}{N}\right)^{3/2} B(m)\right]$$



$N \log[\ldots]$ → linearly on particle #, logarithmically on N/V, E/N, etc.

$B(m)$ → constant

$\Rightarrow$ For historical reasons, conventional to define:

Entropy $S = k \log \Omega$

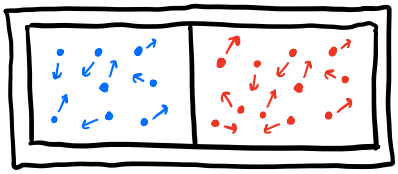
k → Boltzmann's constant (1.38×10^{-23} J/K)

(Note: we'll call $\log \Omega$ "entropy" as well...)

What can we use these results for?

(1) What happens if we bring 2 systems into contact?

⇒ e.g. suppose 2 systems can exchange energy



subsystem 1 N_1, V_1, E_1 subsystem 2 N_2, V_2, E_2

but volume & particle # are each held fixed...

⇒ individual subsystems not closed (E_1 & E_2 can change)

⇒ total system is closed w/ $E_1 + E_2 = E = \text{const}$

⇒ How do we calculate $\Omega(N_1, V_1, N_2, V_2, E) \equiv$ total # microstates?

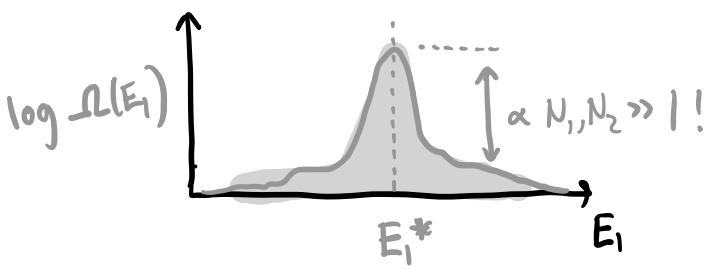
$$\Omega_{tot} = \sum_{E_1} \Omega_1(N_1, V_1, E_1) \times \Omega_2(N_2, V_2, E - E_1)$$

$\Rightarrow$ sometimes call E_1 a "macrostate" i.e. collection of microstates w/ a common property

$$\Rightarrow \Omega(E_1) \equiv \Omega_1(N_1,V_1,E_1)\,\Omega_2(N_2,V_2,E-E_1)$$

# of microstates associated w/ macrostate E_1

$$\text{probability of } E_1 = \frac{\Omega(E_1)}{\Omega_{tot}} \propto \exp\Big[\underbrace{\log\Omega_1(N_1,V_1,E_1) + \log\Omega_2(N_2,V_2,E-E_1)}_{\log\Omega(E_1) = \text{ entropy of macrostate } E_1}\Big]$$



$\Rightarrow$ probability will be sharply peaked around state w/ max $\log\Omega(E)$!

"maximum entropy"

$$\Rightarrow \text{occurs when } 0 = \frac{\partial \log\Omega(E_1)}{\partial E_1} = \frac{\partial \log\Omega_1}{\partial E_1} + \frac{\partial \log\Omega_2(E-E_1)}{\partial E_1}$$

$$\frac{\partial \log\Omega_2}{\partial E_2}\,\cancelto{-1}{\frac{\partial(E-E_1)}{\partial E_1}}$$

$$\Rightarrow \frac{\partial \log \Omega_1}{\partial E_1} = \frac{\partial \log \Omega_2}{\partial E_2}$$

$\Rightarrow$ so special that given a name:

$$\frac{\partial \log \Omega}{\partial E} \equiv \frac{1}{kT}$$

T: Temperature (measured in K)

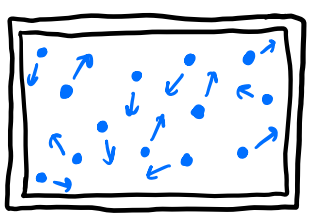
k: Boltzmann's constant

Example: for ideal gas, $\log \Omega = N \log\left(\frac{V}{N}\left(\frac{E}{N}\right)^{3/2} B(m)\right)$

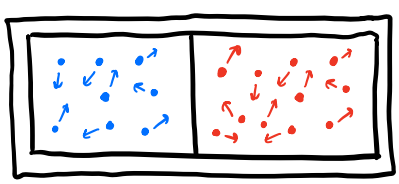
$$\Rightarrow \frac{1}{kT} = \frac{\partial \log \Omega}{\partial E} = \frac{3}{2} N \times \frac{1}{E}$$

$$\Rightarrow kT = \frac{2}{3}\frac{E}{N}$$

(avg energy per particle)



$\Rightarrow$



subsystem 1: N_1, V_1, E_1

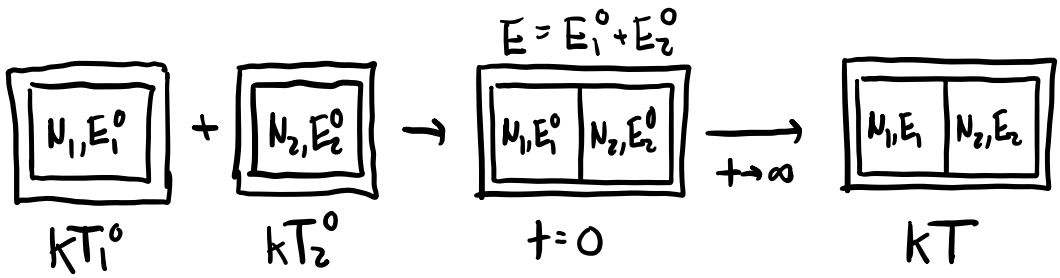
subsystem 2: N_2, V_2, E_2

If temps are equal:

$$\Rightarrow \frac{E_1}{N_1} = \frac{E_2}{N_2}$$

⇒ if gases exchange energy, will reach equilibrium where <u>total</u> energies not equal ($E_1 \neq E_2$), but but <u>energy per particle</u> is ($E_1/N_1 = E_2/N_2$)

⇒ can use to predict what will happen over time:



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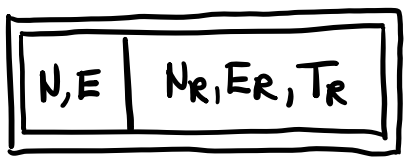
⇒ $\frac{E_1}{N_1} = \frac{E - E_1}{N_2}$ ⇒ $kT = \frac{N_1 kT_1^\circ + N_2 kT_2^\circ}{N_1 + N_2}$

⇒ corollary: if $N_2 \gg N_1 \gg 1$

⇒ $T \approx T_R$



"focal system" (e.g. cell)

"reservoir" (e.g. test tube)

⇒ easy way to bring <u>focal system</u> to well-defined Temp T

$\Rightarrow$ prob of any single microstate for focal system is

$$p_s = \frac{(1)\times \Omega_R(E-E_s)}{\Omega_{tot}(E)} = \exp\left[\log\Omega_R(E-E_s) - \log\Omega(E)\right]$$

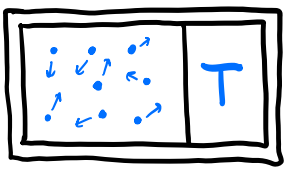
(E_s: smaller than E)

$$\approx \exp\left[\log\Omega_R(E) - \frac{d\log\Omega_R}{dE_R}\cdot\frac{1}{kT}\,E_s - \log\Omega(E) + \dots\right]$$

$$\Rightarrow \quad p_s = \frac{e^{-E_s/kT}}{Z}$$

- E_s: energy of microstate s
- T: temperature of reservoir
- Z: normalization const $\equiv \sum_s e^{-E_s/kT}$ ("Boltzmann factor")

known as **Boltzmann distribution**



(describes systems @ thermal equilibrium)

Example: ideal gas

$$Z = \frac{1}{N!}\sum_{\vec{x}_1}\sum_{\vec{p}_1}\cdots\sum_{\vec{x}_N}\sum_{\vec{p}_N} e^{-\sum_{i=1}^{N}\frac{\vec{p}_i^{\,2}}{2mkT}} = \frac{1}{N!}\left[\sum_{\vec{x},\vec{p}} e^{-\frac{\vec{p}^{\,2}}{2mkT}}\right]^N$$

("Boltzmann factor"; $\sum_{\vec{x},\vec{p}}$: single particle Z_1)

$\Rightarrow$ can do sum: (supplemental notes)

$$\log Z(N,V,T) = N \log\left(\frac{V}{N} \cdot c_0(T) \cdot e\right)$$

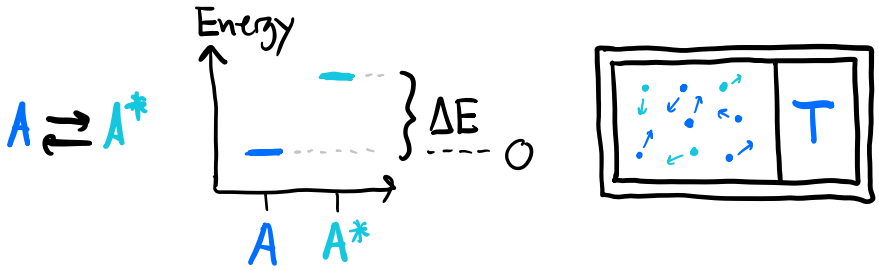
$e \approx 2.71282$

$c_0(T)$: constant (units of concentration)

$\Rightarrow$ can then calculate $p_s = \frac{e^{-E_s/kT}}{Z}$ ...

$\Rightarrow$ Boltzmann dist'n tells us how energy minimization ("classical" physics) competes w/ thermal noise

$\Rightarrow$ can see w/ example: ideal gas w/ internal state



$\Rightarrow$ consider macrostate = single particle is in state A^* (vs A)

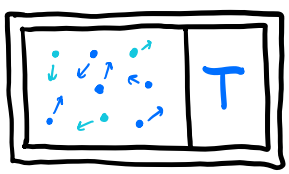
$\Rightarrow$ if $N=1$:

$$\frac{p(A^+)}{p(A)} = \frac{\sum_{s\in A^+} \frac{1}{Z} e^{-E_s/kT}}{\sum_{s\in A} \frac{1}{Z} e^{-E_s/kT}} = \frac{\frac{1}{Z}\left[\sum_{\vec{x},\vec{p}} e^{-\frac{\vec{p}^2}{2mkT}}\right] \times e^{-\frac{\Delta E}{kT}}}{\frac{1}{Z}\left[\sum_{\vec{x},\vec{p}} e^{-\frac{\vec{p}^2}{2mkT}}\right] \times e^{-0}}$$

$$= e^{-\Delta E/kT}$$

Interpretation: states w/ higher energy have lower prob.

but **magnitude** depends on ΔE vs kT!



① if $\Delta E \gg kT \Rightarrow p(A^+) \ll 1$ ("energy wins")

② if $\Delta E \ll kT \Rightarrow p(A^+) \approx p(A) \approx 1/2$ ("entropy/noise wins")

$\Rightarrow$ this is a case where #s matter!

⇒ Some energy scales in **biology**: (Cell Biology by #'s book.bionumbers.org)

@ room temp (~300k) ⇒ $kT \approx 4\times10^{-21}$ J
$(3\times10^{-2}$ eV$)$

How do <u>energies</u> compare to this value?

① mispaired DNA bases ~ $\Delta E \lesssim 4kT$

(A-C-T / T-G-A vs A-C-T / T-C-A) $(P_{err} \gtrsim e^{-4} \approx 0.02)$

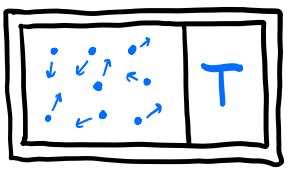
② other hydrogen bonds $\Delta E \sim 2\text{-}12\ kT$
(e.g. transcription factors)

③ ATP hydrolysis ~ 12 kT * (@ 1M conditions)

④ mass of protein ~ 1m off ground: $mgh \sim 0.1\ kT$
$(5\times10^{-23}$ kg$)$

(5) mass of virus ~1m off ground: $mgh \sim 2\times10^{3}\ kT$
($\sim 10^{-18}$ kg)

$\Rightarrow$ in general: $kT \approx$ how much energy can you easily "borrow" from environment



$p_s \propto e^{-\frac{E_s}{kT}}$

$\Rightarrow$ also, how much energy you have to "fight against" to go in opposite direction

$\Rightarrow$ more generally, for macrostate M w/ energy E_M:

$$p(M) = \sum_{s \in M} \frac{e^{-E_s/kT}}{Z} = \frac{1}{Z} \times \Omega_M \times e^{-E_M/kT}$$

Ω_M: # microstates associated w/ M. "entropy"

$\Rightarrow$ $$p(M) = \frac{1}{Z} e^{\log \Omega_M - \frac{E_M}{kT}}$$

i.e. how much energy you can trade off for entropy (or v.v.)

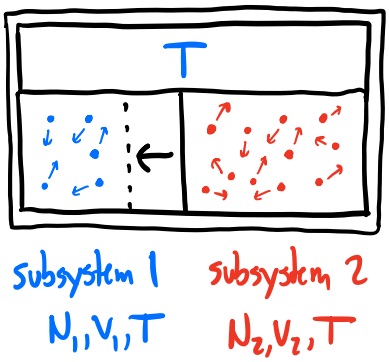
$\Rightarrow$ so far have just exchanged energy....

$\Rightarrow$ can do other things!

E.g. exchange volume & energy

total volume $V = V_1 + V_2$

temperature $T = T_1 = T_2$

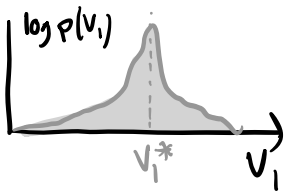


Repeating steps above (macrostate V_1):

$$p(V_1) = \sum_{s \in V_1} \frac{e^{-E_s/kT}}{Z} \propto \underbrace{\frac{1}{N_1!}\left(\sum_{\vec{x} \in V_1} \sum_{\vec{p}} e^{-\frac{\vec{p}^2}{2mkT}}\right)^{N_1}}_{Z_1(N_1, V_1, T)} \underbrace{\frac{1}{N_2!}\left(\sum_{\vec{x} \in V - V_1} \sum_{\vec{p}} e^{-\frac{\vec{p}^2}{2mkT}}\right)^{N_2}}_{Z_2(N_2, V - V_1, T)}$$

$$\propto \exp\Big[\underbrace{\log Z_1(N_1, V_1, T) + \log Z_2(N_2, V - V_1, T)}_{\log Z(V_1)}\Big]$$

$\Rightarrow$ Probability concentrated @ max of



$$\Rightarrow \quad \frac{\partial \log Z_1}{\partial V_1} = \frac{\partial \log Z_2}{\partial V_2} \equiv \frac{p}{kT} \rightarrow \text{definition of "pressure"}$$

$$\Rightarrow \text{ for ideal gas, } \log Z = N \log\left(\frac{V}{N} \cdot c(T) \cdot e\right)$$

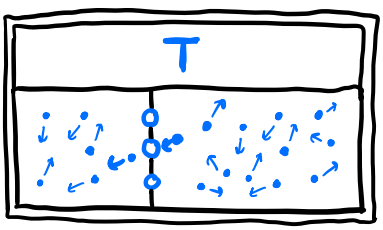
$$\Rightarrow \quad \frac{p}{kT} \equiv \frac{\partial \log Z}{\partial V} = N \times \frac{1}{V}$$

$$\Rightarrow \quad \text{"ideal gas law"} \quad pV = NkT$$

E.g. can also exchange particles:

total particles $N = N_1 + N_2$

temperature $T = T_1 = T_2$



subsystem 1 N_1, V_1, E_1 subsystem 2 N_2, V_2, E_2

$\Rightarrow$ Repeating steps above:

$$\frac{\partial \log Z_1}{\partial N_1} = \frac{\partial \log Z_2}{\partial N_2} \equiv \frac{-\mu}{kT}$$

$\rightarrow$ definition of "chemical potential"

Funny name... but describes something simple:

$\Rightarrow$ Ideal gas: $\log Z = N \log\left(\frac{V}{N} \cdot c_0(T,m) \cdot e\right)$

$$\Rightarrow \frac{-\mu}{kT} = \frac{\partial \log Z}{\partial N} = (1) \cdot \log\left(\frac{V}{N} \cdot c_0(T,m) \cdot e\right) + N \cdot \frac{-1}{N}$$

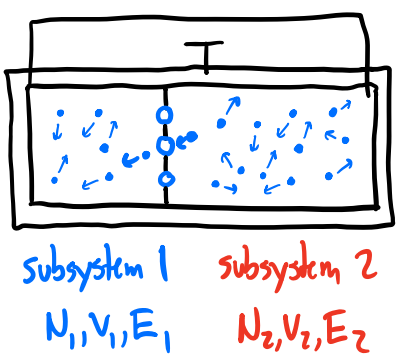
$= \log\left(\frac{1}{e}\right) = -1$

$$\Rightarrow \frac{\mu}{kT} = \log\left(\frac{N}{V} \times c_0(m,T)^{-1}\right)$$

$\frac{N}{V}$: concentration, c ; $c_0(m,T)^{-1}$: constant

$\Rightarrow$ equal chemical potential

= equal concentrations



⇒ can derive analogue of Boltzmann factor:

$$p(M) = \frac{\Omega_M \times \Omega_R(N-N_M, V-V_M, E-E_M)}{\Omega_{tot}}$$

Taylor expand * for $N_M \ll N$, etc.

$$p(M) = \frac{1}{Z} e^{-\left(\frac{E_M + pV_M - \mu N_M - kT \log \Omega_M}{kT}\right)}$$

"free energy"

e.g. how much energy can you trade off for concentration

how much concentration can you "borrow" from envt, etc.

⇒ <u>Next</u>: let's apply these tools to some bio examples...

Supplement: How do we do the $\Omega(N,V,E)$ sum?

From class:

sum over microstates

$$\Omega = \frac{1}{N!} \overbrace{\sum_{\vec{x}_1} \sum_{\vec{p}_1} \cdots \sum_{\vec{x}_N} \sum_{\vec{p}_N}}^{} 1^{\times} \left\{ \begin{array}{l} \vec{x}_i \in V \\ \sum_i \frac{|\vec{p}_i|^2}{2m} = E \end{array} \right\}$$

$\frac{1}{N!}$ → particles are indistinguishable (from QM)

allowed microstates

Step 1: approximate sums (Σ) w/ integrals ($\int dx$)

⇒ need to be a bit careful w/ units...

⇒ imagine space & momentum (time) are divided into grid of discrete values separated by Δx & Δp (e.g. ~ QM)

$$\Rightarrow \sum_x \to \int \frac{dx}{\Delta x} \quad , \quad \sum_p \to \int \frac{dp}{\Delta p}$$

$\Rightarrow$ similarly, minimum energy interval: $\Delta E = \frac{3\Delta p^2}{2m}$

$$\Omega = \frac{1}{N!} \iint\cdots\int \prod_{i=1}^{N} \frac{d^3\vec{x}_i\, d^3\vec{p}_i}{(\Delta x \Delta p)^3} \quad \begin{cases} \vec{x}_i \in V \\ \sum_i \frac{|\vec{p}_i|^2}{2m} \in E \pm \Delta E \end{cases}$$

Step 2: evaluate integrals

$\Rightarrow$ Integrals over $\vec{x}_i$ are "easy" (each one gives factor V)

$$\Rightarrow \Omega = \frac{V^N}{N! \Delta x^{3N}} \int \prod_{i=1}^{N} \frac{d\vec{p}_i}{\Delta p} \text{ s.t. } \sum_i \frac{\vec{p}_i^{\,2}}{2m} \in E \pm \Delta E$$

$\Rightarrow$ Now change variables to $\vec{y}_i = \frac{\vec{p}_i}{\sqrt{2mE}}$ ...

$$\Omega \approx \frac{V^N (2mE)^{\frac{3N}{2}}}{N! (\Delta x \Delta p)^{3N}} \left[\int \prod_{i=1}^{N} d\vec{y}_i \text{ s.t. } \sum_{i=1}^{N} \vec{y}_i^{\,2} \in 1 \pm \frac{\Delta E}{E} \right]$$

$\Rightarrow$ last term $= \frac{\Delta E}{E} \times \frac{\text{surface area of } 3N\text{-dimensional unit sphere}}{F(N)}$

$\Rightarrow$ from Wikipedia: $F(N) = \frac{2 \cdot \pi^{\frac{3N}{2}}}{(\frac{3N}{2}-1)!}$

$$\Rightarrow \Omega(N,V,E) = \frac{V^N (2mE)^{\frac{3N}{2}-1} 2\cdot\pi^{\frac{3N}{2}}}{N!\, 3\Delta x^{3N} (\Delta p)^{3N-2} (\frac{3}{2}N-1)!}$$

$$\Rightarrow \log\Omega = N\log\left(\frac{V}{\Delta x^3}\right) + \left(\frac{3N-1}{2}\right)\log\left(\frac{2\pi m E}{\Delta p^2}\right) + \log\left(\frac{2\pi}{3}\right) - \log N! - \log\left(\frac{3}{2}N-1\right)!$$

Step 3: approximate for large N

$\Rightarrow$ sterling's approx: $\log N! \approx N\log N - N + \mathcal{O}(\log(N))$

(i.e. only keep linear & higher terms in N)

$$\Rightarrow \log\Omega \approx N\log\left(\frac{V}{\Delta x^3}\right) + \frac{3N}{2}\log\left(\frac{2\pi m E}{\Delta p^2}\right)$$

$$- N\log N + N - \frac{3N}{2}\log\left(\frac{3N}{2}\right) + \frac{3N}{2}$$

$$\Rightarrow \log\Omega(N,V,E) \approx N\log\left[\frac{V}{N}\left(\frac{E}{N}\right)^{3/2}\underbrace{\left[\frac{4\pi m}{3}\right]^{3/2}\frac{e^{5/2}}{\Delta x^3 \Delta p^3}}_{B(m)}\right]$$

Supplement 2: How do we do the $Z(N,V,T)$ sum?

From class: $$Z = \frac{1}{N!}\left(\sum_{\vec{x},\vec{p}} e^{-\frac{\vec{p}^2}{2mkT}} \left\{\vec{x}\in V\right\}\right)^N$$

$$\Rightarrow \text{only need } Z_1 \equiv \sum_{\vec{x},\vec{p}} e^{-\frac{\vec{p}^2}{2mkT}} \left\{\vec{x}\in V\right\}!$$

Step 1: approximate sums w/ integrals

$$\Rightarrow Z_1 \approx \int \frac{d^3\vec{x}}{(\Delta x)^3}\cdot\frac{d^3\vec{p}}{(\Delta p)^3} e^{-\frac{|\vec{p}|^2}{2mkT}} \times \left\{x_i\in V\right\}$$

Step 2: evaluate integrals

$$\Rightarrow Z_1 = \frac{V}{\Delta x^3}\times\underbrace{\left(\int_{-\infty}^{\infty}\frac{dp}{\Delta p} e^{-\frac{p^2}{2mkT}}\right)^3}_{\text{Gaussian integral} = \frac{\sqrt{2\pi mkT}}{\Delta p}} = \frac{V}{\Delta x^3}\left(\frac{2\pi mkT}{\Delta p^2}\right)^{3/2}$$

$$\Rightarrow \quad \log Z = N \log\left(\frac{V}{\Delta x^3}\left(\frac{2\pi m k T}{\Delta p^2}\right)^{3/2}\right) - \log N!$$

step 3: approximate for large N ($\log N! \simeq N \log N - N$)

$$\Rightarrow \quad \log Z(N,V,T) = N \log\left(\frac{V}{N} \cdot \underbrace{\left(\frac{2\pi m k T}{\Delta x^2 \Delta p^2}\right)^{3/2}}_{C_0(m,kT)\ \text{(units of concentration)}} \cdot e\right)$$

(note: much easier than calc'n of $\Omega(N,V,E)$!)