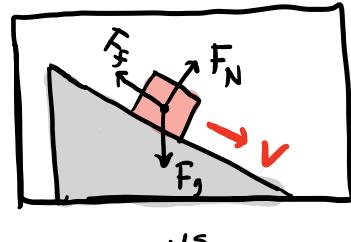


Announcements:

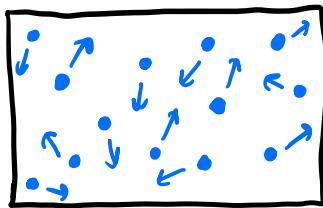
- ① "advanced copy" of today's notes
in Files → Week 1 folder on Canvas
(will fill in a bit as we go)
- ② First feedback assignment posted (due Sat)
- ③ Optional practice problems posted
(Files → Week 1 folder on Canvas)
- ④ "Background on probability" document posted too

Lecture 2 : Introduction/Review of Statistical Mechanics

* Stat mech = set of tools to :



vs



- 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 :

$\sim 10^6$ proteins
 $\sim 10^4$ ribosomes

- ② thermal noise is important for design

& function of many cellular processes

\Rightarrow statmech is usually subject of whole course

\Rightarrow will give abbreviated intro / review today

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

For longer intro to stat mech in biology,

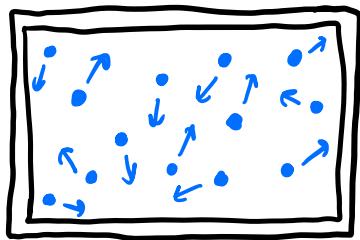
see Chapters 5&6 of Physical Biology of the Cell

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 → "microstates"
occur w/ equal probability

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

\Rightarrow Why is this true?!?

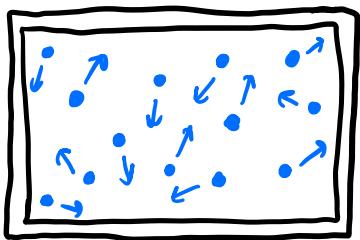
\Rightarrow Deep question! (tricky to prove in general...)

\Rightarrow Here, will treat as assumption

\Rightarrow Key Question: What is a microstate?

& how do we count them?

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



$\Rightarrow N$ particles of mass m

\Rightarrow confined to box of size V

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

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

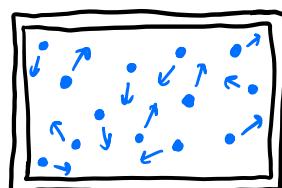
\Rightarrow Microstate, $s = (\vec{x}_1, \vec{p}_1, \vec{x}_2, \vec{p}_2, \dots, \vec{x}_N, \vec{p}_N)$

$\Rightarrow 6N$
total
variables

\Rightarrow which microstates are allowed?

① $N = \text{const}$

② $\vec{x}_i \in V = \text{const}$



+

③ Physics:

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

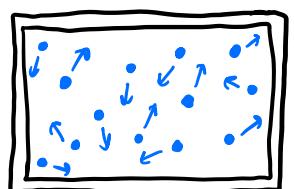
Counting microstates: total # of microstates, $\Omega(N,V,E)$

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

↳ particles are
indistinguishable (from QM) ↳ allowed microstates

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

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



↳ linearly on particle #
 logarithmically on N/V , E/N , etc.

\Rightarrow For historical reasons, conventional to define:

$$\text{Entropy } S = k \log \Omega$$

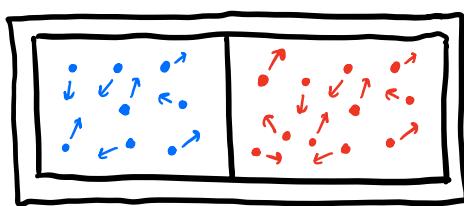
↳ Boltzmann's constant
 $(1.38 \times 10^{-23} \text{ J/K})$

(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 Subsystem 2
 N_1, V_1, E_1 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 $\mathcal{L}(N_1, V_1, N_2, V_2, E) \equiv \frac{\text{total \# microstates}}{\text{microstates}}$?

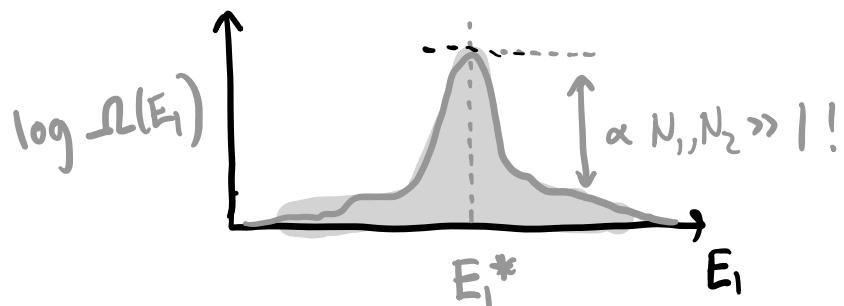
$$\mathcal{L}_{\text{tot}} = \sum_{E_1} \underbrace{\mathcal{L}_1(N_1, V_1, E_1) \cdot \mathcal{L}_2(N_2, V_2, E - E_1)}_{\mathcal{L}(E_1)}$$

\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

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



\Rightarrow probability will be sharply peaked
 around state w/ $\max \log \Omega(E_1)$!

"maximum entropy"

$$\Rightarrow \text{occurs when } 0 = \frac{d \log \Omega(E_1)}{d E_1} = \frac{d \log \Omega_1}{d E_1} + \cancel{\frac{d \log \Omega_2}{d E_1}} - 1$$

$$\frac{d \log \Omega_2}{d E_2} \frac{d}{d E_1} (E - E_1)$$

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

\Rightarrow so special that given a name:

$$\frac{\partial \log \Omega}{\partial E} = \frac{1}{kT} \quad \begin{array}{l} \text{Temperature} \\ \text{(measured in K)} \end{array}$$

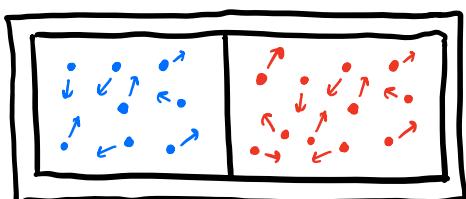
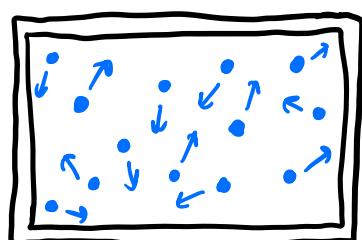
Boltzmann's constant

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

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

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

(avg energy per particle)



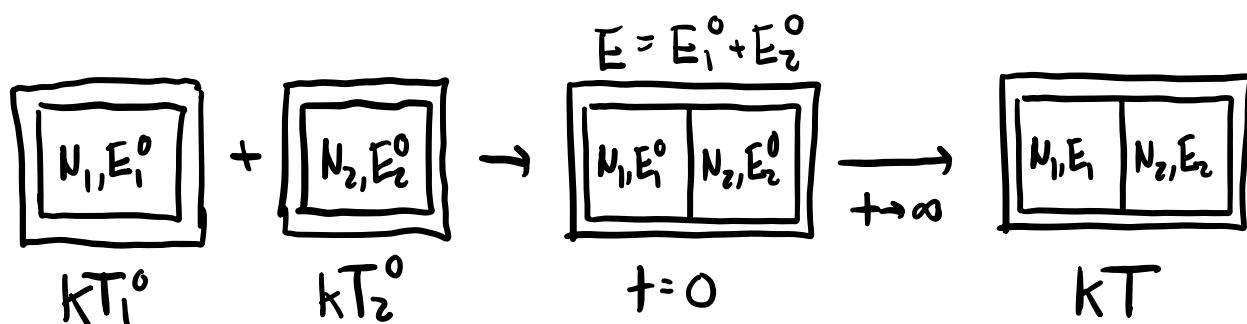
Subsystem 1 Subsystem 2
 N_1, V_1, E_1 N_2, V_2, E_2

If temps are equal:

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

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

\Rightarrow can use to predict what will happen over time:



$$\Rightarrow \frac{E_1}{N_1} = \frac{E - E_1}{N_2} \Rightarrow kT = \frac{N_1 kT_1^0 + N_2 kT_2^0}{N_1 + N_2}$$

\Rightarrow corollary: if $N_2 \gg N_1$

$$\Rightarrow T \approx T_R$$



"focal system" (e.g. cell) "reservoir" (e.g. test tube)

\Rightarrow easy way to bring focal system to well-defined Temp T

\Rightarrow prob of any single microstate for focal system is

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

smaller than E

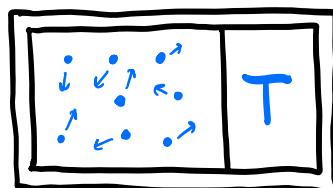
$$\approx \exp \left[\log \Omega_R(E) - \frac{1}{kT} E_s - \log \Omega(E) + \dots \right]$$

Boltzmann factor.

$$\Rightarrow p_s = \frac{e^{-E_s/kT}}{Z} \quad \begin{array}{l} \text{--- energy of microstate } s \\ \text{--- } kT \leftarrow \text{temperature of reservoir} \\ \text{--- } Z \leftarrow \text{normalization const} \equiv \sum_s e^{-E_s/kT} \end{array}$$

known as

Boltzmann distribution



(describes systems @ thermal equilibrium)

Example: ideal gas Boltzmann factor:

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

$$\Rightarrow \text{can do sum: } \log Z(N, V, T) = N \log \left(\frac{V}{N} \cdot c_0(T) \cdot e \right)$$

(supplemental notes)

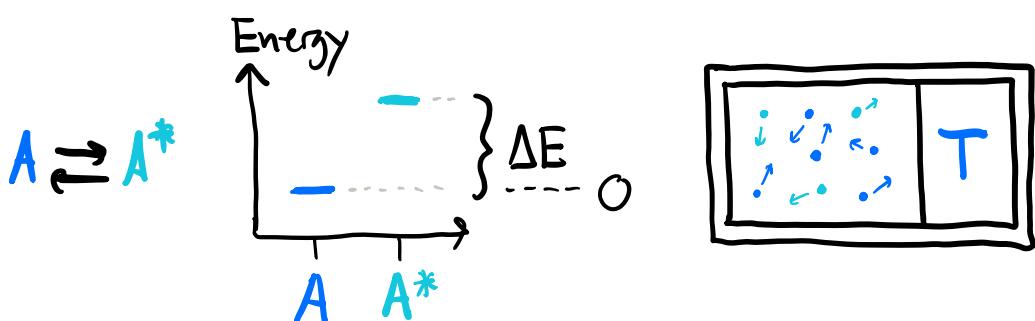
constant
(units of concentration)

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

\Rightarrow Boltzmann dist'n tells us how energy minimization



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



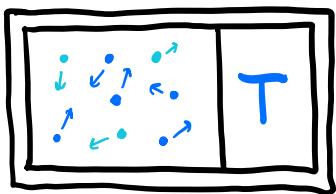
\Rightarrow consider macrostate = single particle is in state A^* (vs A)

\Rightarrow if $N=1$:

$$\frac{p(A^*)}{p(A)} = \frac{\sum_{s \in A^*} \frac{1}{Z} e^{-E_s/kT}}{\sum_{s \in A} \frac{1}{Z} e^{-E_s/kT}} = \frac{\cancel{\frac{1}{Z} \left[\sum_{\substack{s \\ s \neq A^*}} e^{-\frac{E_s - E_{A^*}}{kT}} \right]} \times e^{-\frac{\Delta E}{kT}}}{\cancel{\frac{1}{Z} \left[\sum_{\substack{s \\ s \neq A^*}} e^{-\frac{E_s - E_{A^*}}{kT}} \right]} \times e^0}$$

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

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 $\Delta E \ll kT \Rightarrow p(A^*) \approx p(A) \approx \frac{1}{2}$ ("entropy/noise wins")

\Rightarrow this is a case where #s matter!

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

$$@ \text{room temp } (\sim 300\text{K}) \Rightarrow kT \approx 4 \times 10^{-21} \text{ J}$$
$$(3 \times 10^{-2} \text{ eV})$$

How do energies compare to this value?

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

$$\left(\begin{array}{c} \text{A-C-T} \\ | \\ \text{T-G-A} \end{array} \text{ vs } \begin{array}{c} \text{A-C-T} \\ | \\ \text{T-C-A} \end{array} \right) \Rightarrow P_{\text{err}} \gtrsim e^{-\frac{4kT}{\Delta E}} \sim e^{-4} \sim 0.02$$

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

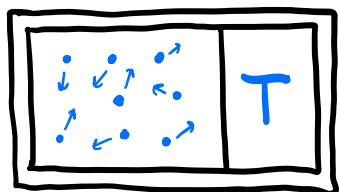
③ ATP hydrolysis $\sim 12 kT^*$ (@ 1M conditions)

④ mass of protein $\sim 1\text{m off ground}$: $mgh \sim 0.1 kT$
 $(5 \times 10^{-23} \text{ kg})$

$$\begin{array}{c} \uparrow \\ \text{F}_g = mg \\ \left. \right\} h \end{array}$$

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

\Rightarrow in general: $\text{kT} \approx$ 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 particular direction

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

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

\downarrow # microstates associated w/ M .

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

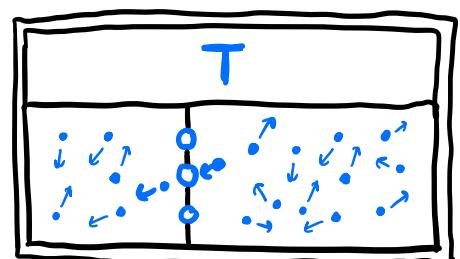
i.e. how much energy you can trade off for entropy (or v.v.)

\Rightarrow so far have just exchanged energy....
 \Rightarrow can do other things!

E.g: can exchange energy + particles:

$$\text{total particles } N = N_1 + N_2$$

$$\text{temperature } T = T_1 = T_2$$



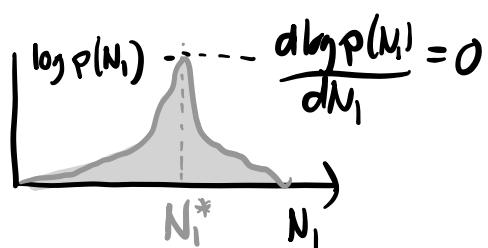
$$\begin{array}{ll} \text{subsystem 1} & \text{subsystem 2} \\ N_1, V_1, E_1 & N_2, V_2, E_2 \end{array}$$

Repeating steps above (macrostate N_1):

$$p(N_1) = \sum_{S \in N_1} \frac{e^{-E_S/kT}}{Z} \propto \underbrace{\frac{1}{N_1!} \left(\sum_{\vec{x} \in V_1} \sum_{\vec{p}} e^{-\frac{\vec{p}^2}{2mkT}} \right)^{N_1}}_{Z_1(N_1, V_1, T)} \underbrace{\frac{1}{(N-N_1)!} \left(\sum_{\vec{x} \in V_2} \sum_{\vec{p}} e^{-\frac{\vec{p}^2}{2mkT}} \right)^{N-N_1}}_{Z_2(N-N_1, V_2, T)}$$

$$\propto \exp \left[\log Z_1(N_1, V_1, T) + \log Z_2(N-N_1, V_2, T) \right]$$

\Rightarrow Probability concentrated @ max of



\Rightarrow Repeating steps above:

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

definition of
"chemical potential"

Funny name... but describes something simple:

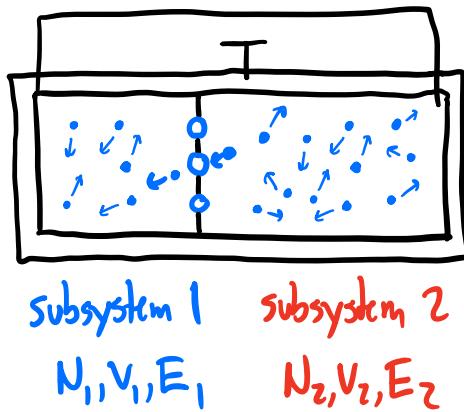
$$\Rightarrow \text{Ideal gas: } \log Z = N \log \left(\frac{V}{N} \cdot C_0(T, m) \cdot e \right)$$

$$\Rightarrow -\frac{\mu}{kT} = \frac{\partial \log Z}{\partial N} = (1) \cdot \log \left(\frac{V}{N} \cdot C_0(T, m) \cdot e \right) + N \cdot \frac{-1}{\mu}$$

$$\Rightarrow \frac{\mu}{kT} = \log \left(\frac{N}{V} \times C_0(m, T)^{-1} \right)$$

concentration, c constant

\Rightarrow equal chemical potential
= equal concentrations



\Rightarrow can derive analogue of Boltzmann factor:

$$p(M) = \sum_{\substack{S_S \in M \\ S_R \in N - N_M}} \frac{e^{-\frac{E_S(S_S) + E_R(S_R)}{kT}}}{Z_{\text{tot}}} \propto \frac{N_M e^{-\frac{E_M}{kT}} \cdot Z_R(N - N_M)}{Z_{\text{tot}}}$$

\Rightarrow Taylor expand for $N_M \ll N_{\text{tot}}$:

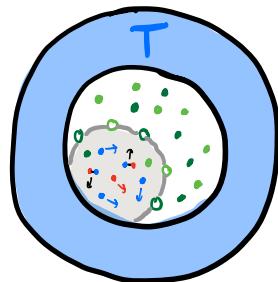
$$p(M) = \frac{1}{Z} e^{-\frac{(E_M - \mu N_M - kT \log Z_M)}{kT}}$$

Tells us:

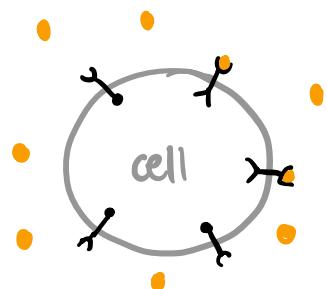
e.g. how much energy can you trade off for concentration
how much concentration can you "borrow" from envt, etc.

\Rightarrow Next: let's apply these tools to some bio examples...

① How do cells build costly molecules?



② How do cells measure their environment?



Supplement: How do we do the $\mathcal{L}(N,V,E)$ sum?

From class:

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

particles are indistinguishable (from QM) allowed microstates

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

\Rightarrow need to be a bit careful w/ units...

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

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

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

$$\Omega = \frac{1}{N!} \iint \dots \int \prod_{i=1}^N \frac{d^3 \vec{x}_i d^3 \vec{p}_i}{(\Delta x \Delta p)^3} \quad \left\{ \begin{array}{l} \vec{x}_i \in V \\ \sum_i \frac{|\vec{p}_i|^2}{2m} \in E \pm \Delta E \end{array} \right.$$

Step 2: evaluate integrals

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

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

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

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

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

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

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

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

Step 3: approximate for large N

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

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

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

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

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

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

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

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

Step 1: approximate sums w/ integrals

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

Step 2: evaluate integrals

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

$$\text{(Gaussian integral)} = \frac{\sqrt{2\pi mkT}}{\Delta p}$$

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

Step 3: approximate for large N ($\log N! \approx N \log N - N$)

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

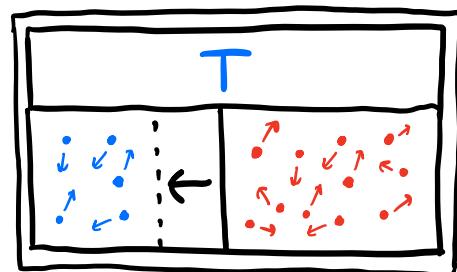
$C_0(m, kT)$ (units of concentration)

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

Supplement 3: Exchanging volume & energy

total volume $V = V_1 + V_2$

temperature $T = T_1 = T_2$



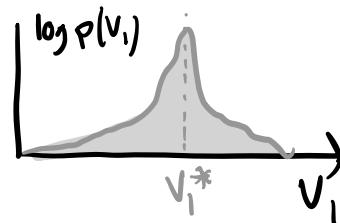
Subsystem 1 Subsystem 2
 N_1, V_1, T N_2, V_2, T

Repeating steps above (macrostate V_1):

$$p(V_1) = \sum_{S \in V_1} \frac{e^{-E_S/kT}}{Z} \propto \frac{1}{N_1!} \left(\sum_{\vec{x} \in V_1} \sum_{\vec{p}} e^{-\frac{\vec{p}^2}{2mkT}} \right)^{N_1} \frac{1}{N_2!} \left(\sum_{\vec{x} \in V - V_1} \sum_{\vec{p}} e^{-\frac{\vec{p}^2}{2mkT}} \right)^{N_2}$$

$$\propto \exp \left[\log Z_1(N_1, V_1, T) + \log Z_2(N_2, V - V_1, T) \right]$$

\Rightarrow Probability concentrated @ max of



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

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

$$\Rightarrow \frac{P}{kT} \equiv \frac{\partial \log Z}{\partial V} =$$

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