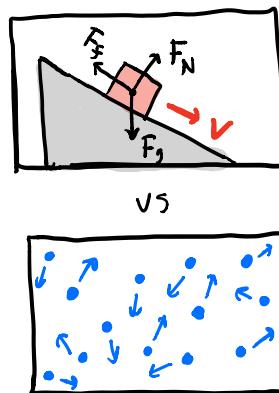


Lecture 3 : Introduction/Review of Statistical Mechanics

* Stat mech = set of tools to :

- 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 :

~ 10^6 proteins
~ 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,

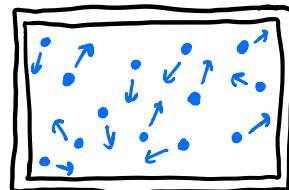
see Chapters 5+6 of Physical Biology of the Cell

Plan: today = basic framework

next time = bio applications

Fundamental Principle of Stat Mech :

In a closed system at equilibrium



⇒ all allowed states of system → "microstates"
occur w/ equal probability

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

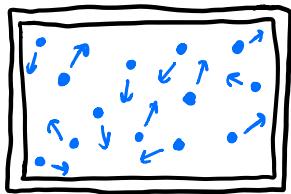
⇒ Why is this true?!?

⇒ Deep question! (tricky to prove in general...)

⇒ Here, will treat as assumption

⇒ Key Question: What is a microstate?
+ how do we count them?

Example: "Ideal Gas" = "collection of barely 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

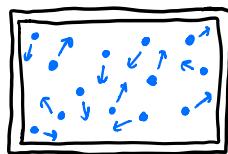
\Rightarrow Which microstates are allowed?

① $N = \text{const}$

② $\vec{x}_i \in V = \text{const}$

+

③ Physics:



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

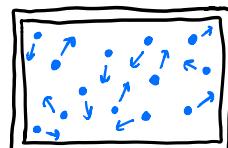
Counting microstates: total # of microstates, $\Omega(N,V,E)$

$$\Omega = \frac{1}{N!} \iiint \dots \int \prod_{i=1}^N \frac{d\vec{x}_i d\vec{p}_i}{h_0^3} \quad \text{s.t.} \quad \left\{ \begin{array}{l} \vec{x}_i \in V \\ \sum_i \frac{|\vec{p}_i|^2}{2m} = E \end{array} \right.$$

indistinguishable (from QM) → for units

⇒ this is an integral we can solve! (supplemental notes)

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



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

⇒ For historical reasons, conventional to define:

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

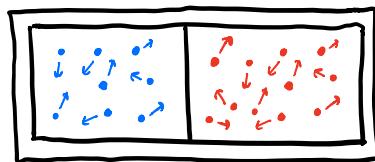
Boltzmann's constant
($1.38 \times 10^{-23} \text{ J/K}$)

(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?

\Rightarrow 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...

\Rightarrow individual subsystems not closed ($E_1 + E_2$ can change)

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

\Rightarrow From definition of $\mathcal{L}(N_1, V_1, N_2, V_2, E)$

$$\mathcal{L} = \frac{1}{N_1! N_2!} \left(\prod_{i=1}^{N_1} \frac{d\vec{x}_i d\vec{p}_i}{h_0^3} \right) \cdot \left(\prod_{j=1}^{N_2} \frac{d\vec{x}_j d\vec{p}_j}{h_0^3} \right) \text{ s.t. } \begin{cases} \vec{x}_i \in V_1, \vec{x}_j \in V_2 \\ \sum_{i=1}^{N_1} \frac{|\vec{p}_i|^2}{2m_1} + \sum_{j=1}^{N_2} \frac{|\vec{p}_j|^2}{2m_2} = E \end{cases}$$

\Rightarrow can rewrite as sum over E_1 :

$$\Omega = \int_0^E dE_1 \left[\underbrace{\frac{1}{N_1!} \int_i \frac{\prod dx_i d\vec{p}_i}{h^3} \left\{ \vec{x}_i \in V_1, \sum_i \frac{\vec{p}_i^2}{2m_i} = E_1 \right\}}_{\Omega_1(N_1, V_1, E_1)} \right] \left[\underbrace{\frac{1}{N_2!} \int_i \frac{\prod dx_j d\vec{p}_j}{h^3} \left\{ \vec{x}_j \in V_2, \sum_j \frac{\vec{p}_j^2}{2m_j} = E - E_1 \right\}}_{\Omega_2(N_2, V_2, E - E_1)} \right]$$

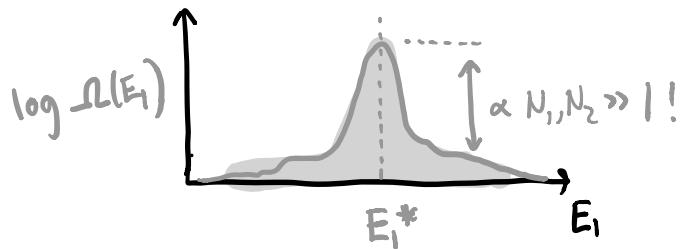
$$\Omega(E_1) = \Omega_1(N_1, V_1, E_1) \Omega_2(N_2, V_2, E - E_1)$$

↓

probability of having E_1 \Leftarrow # microstates corresponding to "macrostate" w/ E_1 in subsystem 1, $E - E_1$ in subsystem 2

$$\Omega = \int_0^E dE_1 \exp \left[\underbrace{\log \Omega_1(N_1, V_1, E_1) + \log \Omega_2(N_2, V_2, E - E_1)}_{\log \Omega(E_1)} \right] \} \text{ probability of } E_1$$

$\log \Omega(E_1) = \text{entropy of macrostate } E_1$



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

"maximum entropy"

$$\Rightarrow \frac{d \log \Omega(E_1)}{d E_1} = \frac{d \log \Omega_1(E_1)}{d E_1} + \frac{d \log \Omega_2(E-E_1)}{d E_2} (-1) = 0$$

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

\Rightarrow so special that
given a name:

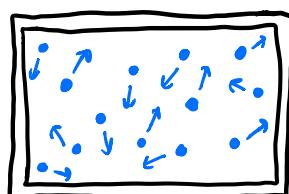
$$\frac{d \log \Omega}{d E} \equiv \frac{1}{kT} \quad \begin{matrix} \text{Temperature} \\ \text{(measured in K)} \\ \hookrightarrow \text{Boltzmann's constant} \end{matrix}$$

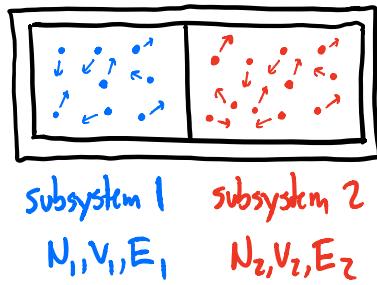
$$\Rightarrow \text{For ideal gas, } \ln \Omega = N \log \left(\frac{V}{N} \left(\frac{E}{N} \right)^{\frac{3}{2}} C(m) \right)$$

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

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

(avg energy per particle)



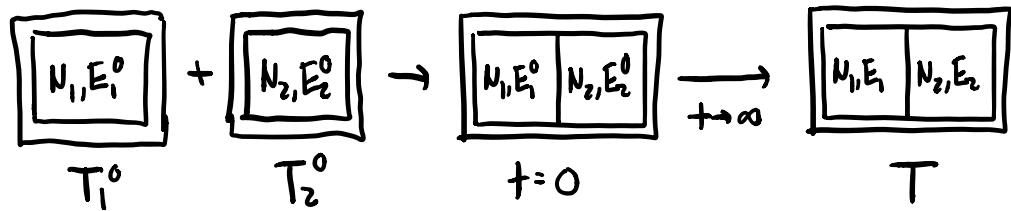


If temps are equal:

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

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

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



$$\Rightarrow \frac{E_1}{N_1} = \frac{E - E_1}{N_2} \Rightarrow kT = \frac{N_1 k T_1^0 + N_2 k T_2^0}{N_1 + N_2}$$

$$= \frac{3}{2} kT$$

\Rightarrow corollary: if $N_2 \gg N_1 \gg 1$

$$\Rightarrow T \approx T_R$$

N, E	N_R, E_R, T_R
--------	-----------------

"system" "reservoir"
(e.g. cell)

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

\Rightarrow prob of any single microstate for (sub)system is:

$$P_S = \frac{(1) \times \Omega_R(E - E_S)}{\Omega(E)} = \exp \left[\log \Omega_R(E - E_S) - \log \Omega(E) \right]$$

$\frac{1}{kT}$ ↑
smaller than E

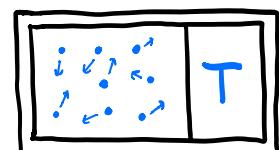
$$\approx \exp \left[\log \Omega_R(E) - \frac{d \log \Omega_R}{dE} E_S - \log \Omega(E) \right]$$

$\Rightarrow P_S = \frac{e^{-E_S/kT}}{Z}$

energy of microstate S
 kT ← temperature of reservoir
 Z ← normalization const (similar to Ω)

known as

Boltzmann distribution

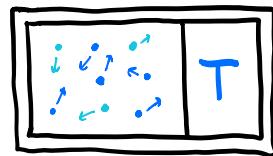


(describes systems @ thermal equilibrium)

\Rightarrow tells us how energy minimization ("classical" physics) competes w/ thermal noise

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

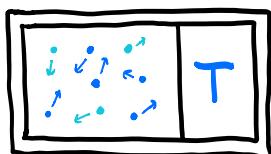
$$A \rightleftharpoons A^* (+\Delta E)$$



\Rightarrow prob of single particle in A vs A^* :

$$\frac{p(A^*)}{p(A)} = \frac{\cancel{\int} e^{-\frac{\Delta E}{kT}} \times \int \frac{d\vec{x} d\vec{p}}{h^3} e^{\frac{-\vec{p}^2}{2m/kT}}}{\cancel{\int} e^{f_0} \times \int \frac{d\vec{x} d\vec{p}}{h^3} e^{\frac{-\vec{p}^2}{2m/kT}}} = e^{-\Delta E/kT}$$

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

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

\Rightarrow Some energy scales in biology:

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

How do energies compare to this value?

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

$\left(\begin{array}{c} ACT \\ T-G-A \end{array} \text{ vs } \begin{array}{c} A-C-T \\ T-C-A \end{array} \right) \quad (P_{err} \approx e^{-4} \approx 0.02)$

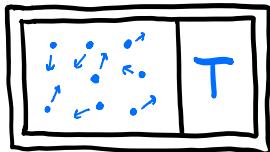
② other hydrogen bonds $\Delta E \sim 2-12 kT$
(e.g. transcription factors)

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

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

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



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

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

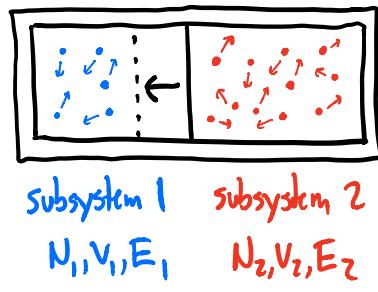
\Rightarrow so far have just exchanged energy....

\Rightarrow can do other things!

E.g. exchange volume & energy

$$\text{total volume } V = V_1 + V_2$$

$$\text{total energy } E = E_1 + E_2$$



Repeating steps above:

$$\Omega = \int dE_1 dV_1 e^{\frac{\log \Omega_1(N_1, V_1, E_1) + \log \Omega_2(N_2, V_2, E - E_1)}{\log \Omega(V, E)}}$$

\Rightarrow Probability concentrated @ joint max of $\log \Omega(V, E)$

$$\Rightarrow \frac{\partial \log \Omega_1}{\partial E_1} = \frac{\partial \log \Omega_2}{\partial E_2} \equiv \frac{1}{kT}$$

$$\frac{\partial \log \Omega_1}{\partial V_1} = \frac{\partial \log \Omega_2}{\partial V_2} \equiv \frac{P}{kT} \rightarrow \begin{matrix} \text{definition of} \\ \text{"pressure"} \end{matrix}$$

$$\Rightarrow \text{for ideal gas : } \log \Omega = N \log \left(\frac{V}{N} \left(\frac{E}{N} \right)^{\frac{3}{2}} C(m) \right)$$

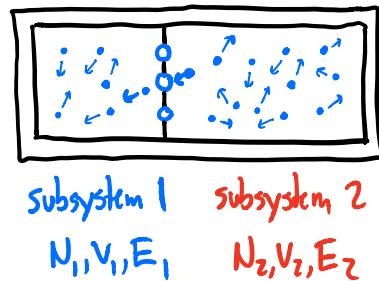
$$\Rightarrow \frac{P}{kT} = \frac{\partial \log \mathcal{L}}{\partial V} = \frac{N}{V}$$

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

E.g. can also exchange energy + particles

$$\text{total energy} \quad E = E_1 + E_2$$

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



Repeating steps above:

$$\frac{\partial \log \mathcal{L}_1}{\partial N_1} = \frac{\partial \log \mathcal{L}_2}{\partial N_2} \equiv \frac{-\mu}{kT} \rightarrow \begin{matrix} \text{definition of} \\ \text{"chemical potential"} \end{matrix}$$

Funny name, but describes something simple:

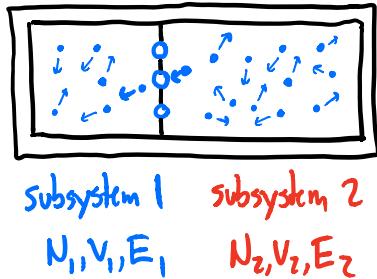
$$\Rightarrow \text{Ideal gas: } \log \mathcal{L} = N \log \left(\frac{V}{N} \left(\frac{E}{N} \right)^{\frac{3}{2}} c(m) \right)$$

$$\Rightarrow -\frac{\mu}{kT} = \frac{\partial \log \Omega}{\partial N} = \log \left(\frac{V}{N} \left(\frac{E}{N} \right)^{\frac{3}{2}} C(m) \right) - \frac{S}{2}$$

$$\Rightarrow \frac{\mu}{kT} = \log \left(\frac{N}{V} \times \underset{\text{concentration}, c}{\underset{\uparrow}{C(m,T)}}^{-1} \right)$$

constant

\Rightarrow equal chemical potential
= equal concentrations



\Rightarrow can derive analogue of Boltzmann factor:

$$P_S = \frac{(1) \times \Omega_R(N-N_s, V-V_s, E-E_s)}{\Omega_{\text{tot}}} \quad \text{Taylor expand for } N_s \ll N, \text{ etc.}$$

$$P_S = \frac{1}{Z} e^{-\frac{(E_s + pV_s - \mu N_s)}{kT}}$$

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

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

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

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

From class:

$$\Omega = \frac{1}{N!} \iiint \dots \int \prod_{i=1}^N \frac{d\vec{x}_i d\vec{p}_i}{h_0^3} \quad \text{s.t.} \quad \left\{ \begin{array}{l} \vec{x}_i \in V \\ \sum_i \frac{|\vec{p}_i|^2}{2m} = E \end{array} \right.$$

indistinguishable (from QM) for units

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

$$\Rightarrow \Omega = \frac{V^N}{N! h_0^{3N}} \int \prod_{i=1}^N d\vec{p}_i \quad \text{s.t.} \quad \sum_i \frac{\vec{p}_i^2}{2m} = E$$

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

$$\Omega = \frac{V^N}{N! h_0^{3N}} (2mE)^{\frac{3N}{2}} \left[\int \prod_{i=1}^N d\vec{y}_i \quad \text{s.t.} \quad \sum_{i=1}^N \vec{y}_i^2 = 1 \right]$$

$F(N)$

\Rightarrow the last term depends only on N ,

\Rightarrow can recognize as surface area of $3N$ -dimensional sphere

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

$$\Rightarrow \mathcal{L}(N, V, E) = \frac{V^N (2mE)^{\frac{3N}{2}} 2\pi^{\frac{3N}{2}}}{N! h_0^{3N} (\frac{3}{2}N-1)!}$$

$$\Rightarrow \log \mathcal{L} = N \log V + \frac{3N}{2} \log(2\pi mE) + \log 2 - 3N \log h_0 - \log N! - \log(\frac{3}{2}N-1)!$$

\Rightarrow for large N , can simplify w/

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

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

$$\Rightarrow \log \Omega \approx N \log V + \frac{3N}{2} \log(2\pi m E) - 3N \log h_0$$

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

$$\Rightarrow \log \Omega(N, V, E) \approx N \log \left[\frac{V}{N} \left(\frac{E}{N} \right)^{\frac{3}{2}} \underbrace{\left[\frac{4\pi m}{3} \right]^{\frac{3}{2}} \frac{e^{\frac{5}{2}}}{h_0^3}}_{c(m)} \right]$$