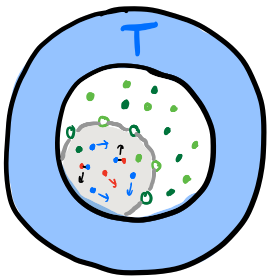
Announcements:

1. advance copy of notes in Week 3 folder on canvas.

2. Solutions for practice problems 1 & 2 posted

3. Will post additional problem for Lectures 4 & 5

Last time: Applications of Equilibrium Statmech

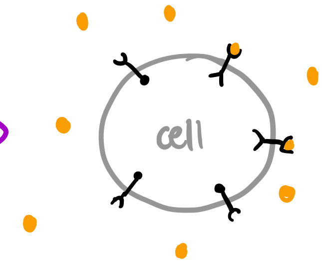


$\Leftarrow$

Boltzmann dist'n

$$p(\vec{s}) \propto e^{-\frac{E(\vec{s})+\mu N(\vec{s})}{kT}}$$

$\Rightarrow$



① How do cells build costly molecules?

② How do cells measure their environment?

* Equilibrium statmech useful for predicting long-term states

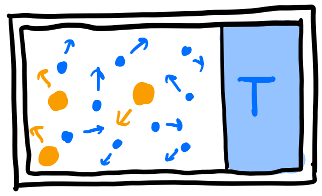
$\Rightarrow$ but timescales are crucial for biology!

(organisms need to react quickly to survive)

$\Rightarrow$ will therefore need tools for predicting dynamics of biophysical systems

One of most important dynamical processes is **diffusion**

⇒ describes dynamics of solute particles floating around in solvent (e.g. ligands, cells, ...) (e.g. H_2O)



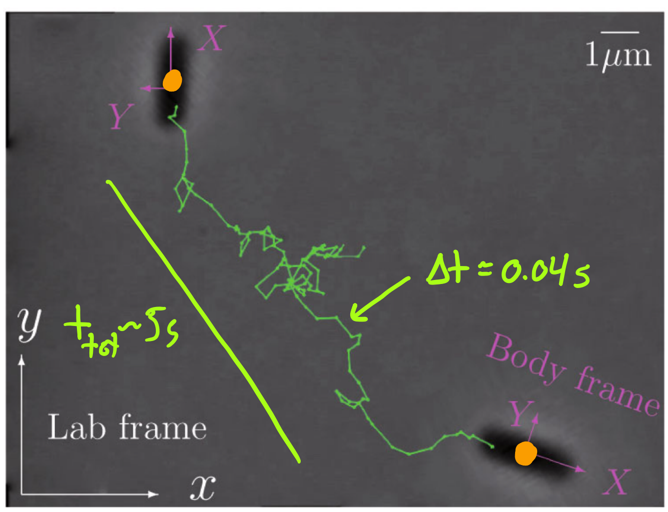
⇒ @ long times, know that system will reach thermal equilibrium

$$p(\vec{s}) \propto e^{-\frac{E(\vec{s})}{kT}}$$

Today: How do solute particles move around w/ time?

Answer: constantly "jiggle around" in (seemingly) random directions

"Brownian motion"

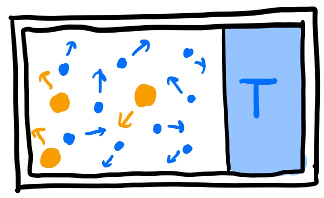


E.g. dead E.coli cell in H_2O
[Tavaddod et al 2010]

⇒ Einstein (+ others) explained how Brownian motion emerges from constant bombardment by solvent molecules (•)

⇒ imposes strong constraints on biology

Today: see how Einstein's argument works in simple model



Next time: applications to sensing + cellular transport

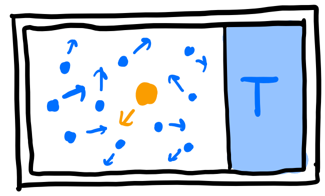
Goal of today's lecture:

① introduce math framework to show how we can understand diffusion in principle

② @ end, can abstract away many details...

⇒ will highlight parts will "use" later (*)

Let's start w/ simple model:

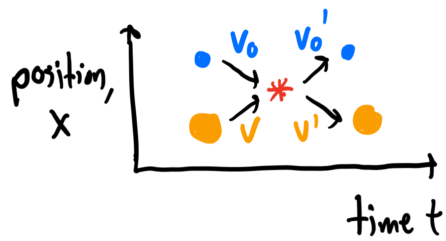


① Solute (●) = N=1 ideal particle w/ mass m

② Solvent (•) = N≫1 ideal particles w/ mass $m_0 \ll m$

③ Elastic collisions between ● + •'s

⇒ for simplicity, start w/ 1D



⇒ simple problem in classical mechanics:

$$v' = \left(1 - \frac{2m_0}{m}\right) v + \frac{2m_0}{m} v_0$$

(supplemental note)

⇒ recursion relation for ● velocity after n collisions:

$$v(n) = \left(1 - \frac{2m_0}{m}\right) v(n-1) + \frac{2m_0}{m} v_0(n)$$

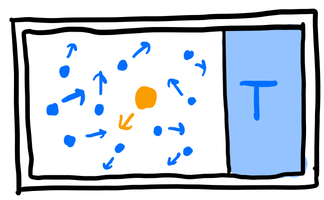
velocity of solute particle in n^{th} collision

↳ velocity right after n^{th} collision

$\Rightarrow$ has exact solution as sum over $v_0(n)$:

$$v(n) = \left(1-\frac{2m_0}{m}\right)^n v(0) + \frac{2m_0}{m}\sum_{j=0}^{n-1}\left(1-\frac{2m_0}{m}\right)^j v_0(n-j)$$

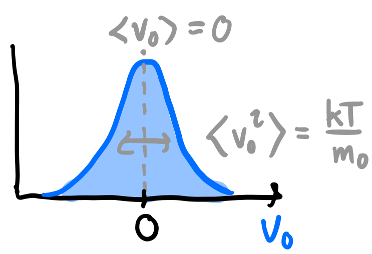
$\Rightarrow$ answer will depend on specific sequence of $v_0(1), v_0(2), \ldots$



Key insight: model these as statistical distribution of independent random variables

① $v_0(n)$ are drawn from Boltzmann dist'n for solvent:

$$p(x_0, v_0) \propto e^{-\frac{E(v_0)}{kT}} = e^{-\frac{m_0 v_0^2}{2kT}}$$



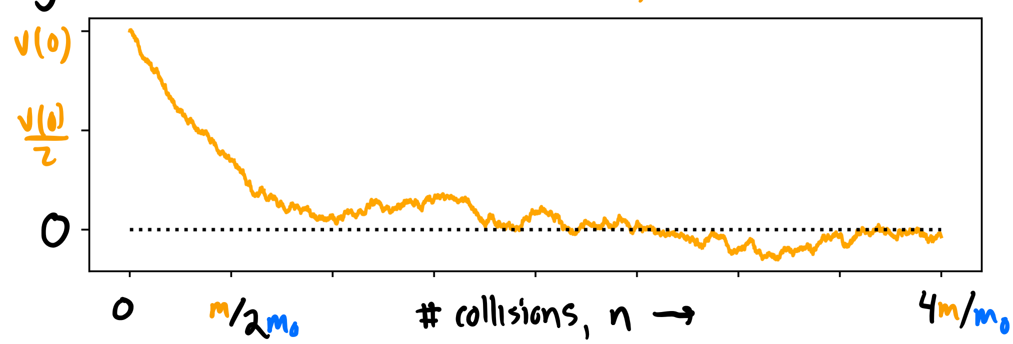
$\Rightarrow$ Gaussian distribution w/ mean $\langle v_0 \rangle = 0$

$+$ variance $\langle v_0^2 \rangle = \dfrac{kT}{m_0}$

(2) Times between collisions are <u>independent</u> of $v(n)$ and have mean $\langle \tau(n) \rangle = \bar{\tau}$

$\tau(n)$ → time between $n-1$ & n^{th} collision

E.g an example trajectory for $v(n)$:



To understand this behavior, let's coarse-grain time into blocks of n_c collisions where $1 \ll n_c \ll \frac{m}{m_0}$

$\Rightarrow$ lots of collisions per block $\Rightarrow$ $\Delta t_b \approx n_c \bar{\tau}$

$\Rightarrow$ within a block, our sol'n for $v(n)$ reduces to

$$v(n_c) - v(0) = -\frac{2m_0}{m} n_c v(0) + \frac{2m_0}{m} \sum_{n=1}^{n_c} v_0(n)$$

(since $n_c \ll m/m_0$) * Taylor expanding in $n \frac{m_0}{m} \ll 1$

or $$\boxed{\Delta v = \underbrace{-\frac{1}{m}\left(\frac{2m_0}{\bar{\tau}}\right)\cdot v\cdot \Delta t_b}_{\Delta V_{drag}} + \underbrace{\frac{2m_0}{m}\sum_{n=1}^{\Delta t_b/\bar{\tau}} v_0(n)}_{\Delta V_{random}}}$$

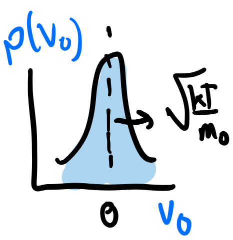
$\Rightarrow$ why "drag"?

$\Rightarrow$ Normally, $F_{drag} = -\gamma\cdot v \iff \Delta V_{drag} = \frac{F_{drag}}{m}\cdot\Delta t = -\frac{\gamma}{m}\, v\,\Delta t$

$\Rightarrow$ $\boxed{\text{drag coefficient } \gamma \equiv \frac{2m_0}{\bar{\tau}}}$

$\Rightarrow$ What about $\Delta V_{random} = \frac{2m_0}{m}\sum_{n=1}^{\Delta t_b/\bar{\tau}} v_0(n)$?

$\Rightarrow$ from properties of Gaussian distribution ΔV_{random} will also be Gaussian w/



$$\langle \Delta V_{random}\rangle = \frac{2m_0}{m}\sum_{n=1}^{\Delta t_b/\bar{\tau}} \langle \cancelto{0}{v_0(n)} \rangle = 0$$

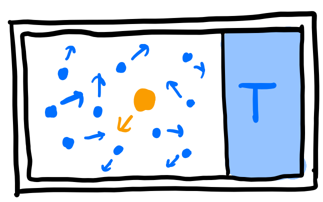
and $$\langle \Delta v_{random}^2 \rangle = \left(\frac{2m_0}{m}\right)^2 \sum_{n=1}^{\Delta t_b/\tau} \langle \cancel{v_0(n)^2} \rangle \xrightarrow{} \frac{kT}{m_0} = \left(\frac{2m_0}{m}\right)^2 \left(\frac{\Delta t_b}{\tau}\right) \frac{kT}{\cancel{m_0}}$$

$$= 2 \cdot \frac{\gamma}{m} \cdot \Delta t_b \cdot \frac{kT}{m}$$

$\Rightarrow$ change in velocity across successive blocks (Δt_b)

$$v(b) = \left(1 - \frac{\gamma \Delta t_b}{m}\right) v(b-1) + \Delta v_{random}(b)$$

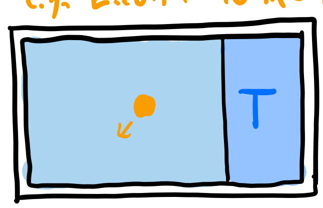
$\Rightarrow$ depends on solvent only through drag coefficient γ!



$\Rightarrow$ Upshot: coarse-grained version (Δt_b) holds for many other models as long as we can predict γ!

E.g. spherical object in liquid:

e.g. E.coli: 10^{-6} m = 1 μm



*** Stokes Law: $\gamma = 6\pi \eta a \leftarrow$ radius of solute

η: viscosity of solvent. [water ~ $10^{-3} \frac{N}{m^2} \cdot s$]

$\Rightarrow$ solution after $b \gg 1$ blocks of time is :

$$\boxed{v(b) = \left(1 - \frac{\gamma \Delta t_b}{m}\right)^b v(0) + \sum_{j=0}^{b-1} \left(1 - \frac{\gamma \Delta t_b}{m}\right)^j \Delta v_{random}(b-j)}$$

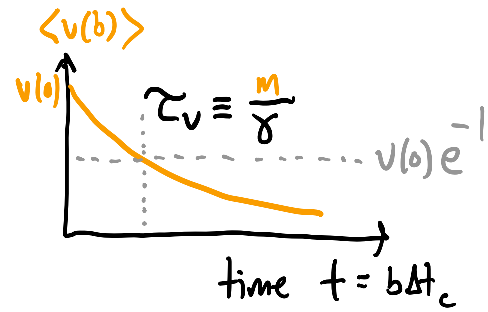
$\Rightarrow$ $\boxed{\text{total time } t = b \cdot \Delta t_b}$

$\Rightarrow$ Can we understand this behavior?

$$\langle v(b) \rangle = \left(1 - \frac{\gamma \Delta t_b}{m}\right)^b v(0) + \sum_{j=0}^{b-1} \left(1 - \frac{\gamma \Delta t_b}{m}\right)^j \cancelto{0}{\langle \Delta v_{random}(b-j) \rangle}$$

$$\langle v(t) \rangle = \left(1 - \frac{\gamma \Delta t_b}{m}\right)^{t/\Delta t_b} v(0)$$

$$\approx e^{-\frac{\gamma t}{m}} \cdot v(0)$$



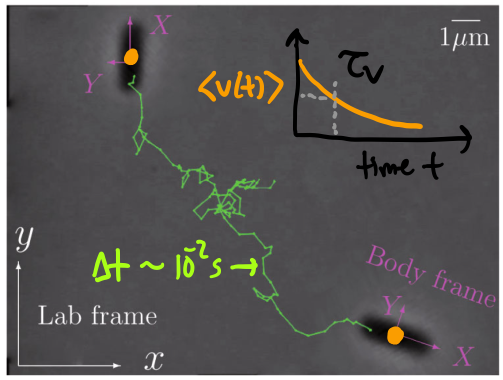
$\Rightarrow$ drag eliminates avg velocity ***

on timescale : $\boxed{\tau_v \equiv \frac{m}{\gamma} = \frac{1}{6\pi\eta}\left(\frac{m}{a}\right)}$

$\Rightarrow$ e.g. for E.coli in H_2O

$$\tau_v \sim \frac{1}{\left(10^{-3}\frac{N\cdot s}{m^2}\right)} \times \left(\frac{10^{-15}\,kg}{10^{-6}\,m}\right)$$

$$\approx 10^{-6}\,s$$



$\Rightarrow$ but actual velocity $v(t) \neq 0$!

Variance:

$$\langle v(b)^2\rangle = \left\langle\left(0 + \sum_{j=0}^{b-1}\left(1-\frac{\gamma\Delta t_c}{m}\right)^j \Delta v_{random}(b-j)\right)^2\right\rangle$$

$$= \sum_{j=0}^{b-1}\sum_{j'=0}^{b-1}\left(1-\frac{\gamma\Delta t_c}{m}\right)^{j+j'}\langle \Delta v_{random}(b-j)\,\Delta v_{random}(b-j')\rangle$$

$$\Downarrow$$

$$= \begin{cases} \langle \Delta v_{random}\rangle^2 & \text{if } j\neq j' \\ \langle \Delta v_{random}^2\rangle & \text{if } j=j' \end{cases}$$

independent random variables

variance = $\sum$ variance$_i$

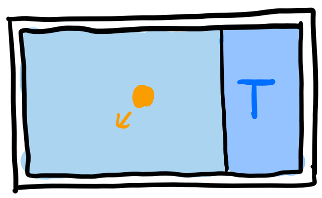
$$= \sum_{j=0}^{b-1}\left(1-\frac{\gamma\Delta t_c}{m}\right)^{2j}\langle \Delta v_{random}^2\rangle \quad \leftarrow \text{geometric series}$$

$$\langle v(t)^2 \rangle = \frac{\cancel{m}}{\cancel{2\gamma\Delta t}} \cdot \underbrace{\langle \Delta v_{random}^2 \rangle}_{2\cancel{\frac{\gamma}{m}}\cancel{\Delta t}\frac{kT}{m}} \cdot \left[1 - \cancel{e^{-\frac{2\gamma}{m}t}}^{\to 0}\right]$$

$$= \frac{kT}{m}$$

$$\Rightarrow \boxed{\langle v(t)^2 \rangle \approx \frac{kT}{m}} \quad \text{when} \quad \boxed{t \gg \tau_v = \frac{m}{\gamma}}$$

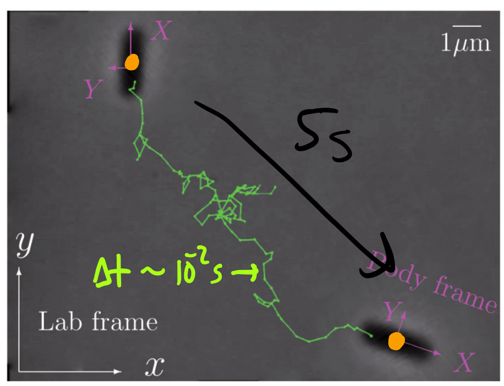
As expected in thermal equilibrium for solute (●)



$\Rightarrow$ for E.coli in H_2O:

$$\sqrt{\langle v^2 \rangle} \sim \left(\frac{4\times10^{-21}\,J}{10^{-15}\,kg}\right)^{1/2}$$

$$\sim 2000\ \mu m/s\ !$$

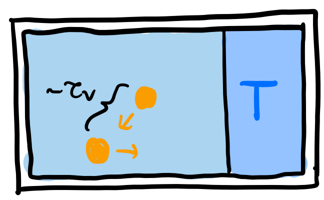


Catch: doesn't stay @ this same velocity for long!

$\Rightarrow$ Can calculate correlations over time:

$$\frac{\langle v(b+j)v(b)\rangle}{\langle v(b^2)\rangle} = \frac{\langle (1-\frac{\gamma\Delta t}{m})^j \cancel{v(b)}\cdot v(b)\rangle}{\langle \cancel{v(b)^2}\rangle} = \left(1-\frac{\gamma\Delta t}{m}\right)^j = e^{-\frac{\gamma}{m}t}$$

$\Rightarrow$ "forgets" previous velocity on timescale $\tau_v = m/\gamma$



$\Rightarrow$ travels distance $\Delta x_v \sim \sqrt{\langle v^2\rangle}\cdot\tau_v$

$\Rightarrow$ for E.coli: $\Delta x_v \sim (10^3\ \mu m/s)\cdot(10^{-6}\,s) \sim 10^{-3}\ \mu m$

Finally, total distance travelled after $b_{tot} = t/\Delta t_b$ blocks

$$x(t) = x(0) + \sum_{b=0}^{t/\Delta t_b - 1} \Delta t_b \cdot v(b)$$

Correlated Gaussians w/ mean + covariance calculated above

$\Rightarrow$ $x(t)$ will also be Gaussian distribution with:

$$\text{mean} \quad \langle x(t) \rangle = x(0) + \sum_{b=0}^{t/t_b - 1} \Delta t_b \cdot \cancel{\langle v(b) \rangle}^{\,0} = x(0)$$

$$\text{and} \quad \langle [x(t) - x(0)]^2 \rangle = \left\langle \left(\sum_{b=0}^{t/\Delta t_b - 1} \Delta t_b \cdot v(b) \right)^2 \right\rangle$$

$$= \Delta t_b^2 \sum_{b,b'}^{t/\Delta t_b - 1} \langle v(b) v(b') \rangle$$

$$= \Delta t_b^2 \sum_{b,b'}^{t/\Delta t_b - 1} \left(1 - \frac{\gamma \Delta t_b}{m}\right)^{|b-b'|} \langle v(b)^2 \rangle$$

(supplemental note)

$$\Rightarrow \langle \Delta x^2 \rangle \approx \cancel{\Delta t_b^2} \cdot \frac{t}{\cancel{\Delta t_b}} \cdot \frac{2\cancel{m}}{\gamma \cancel{\Delta t_b}} \cdot \cancel{\langle v^2 \rangle}^{\frac{kT}{m}} = 2 \cdot \frac{kT}{\gamma} \cdot t$$

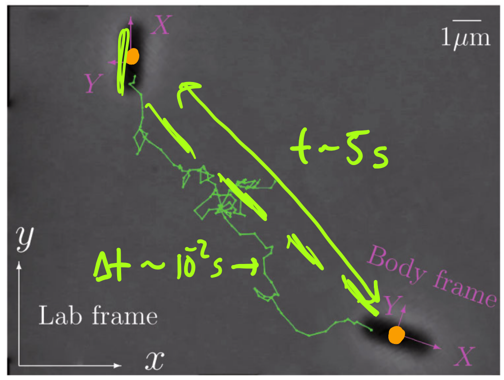
$$\frac{kT}{\gamma} \equiv D \quad \text{"diffusion constant"}$$

when $t \gg \tau_v \equiv m/\gamma$

$\Rightarrow$ **Diffusion coefficient**: $D = \dfrac{kT}{\gamma} = \dfrac{kT}{6\pi\eta a}$ "Einstein relation"

E.g. E. coli in H_2O:

$$D = \frac{4\times10^{-21}\,J}{20\,(10^{-3}\,\frac{N\cdot s}{m^2})(10^{-6}\,m)} = \frac{4\times10^{-13}}{2} \simeq 0.2\times \mu m^2/s$$

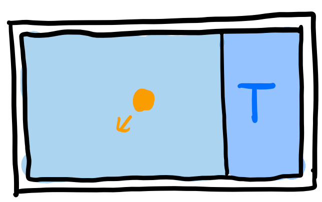


$$\Delta x \sim \sqrt{2\cdot D\cdot 5s} \sim \sqrt{2\,\mu m^2} \sim 1\text{-}2\,\mu m$$

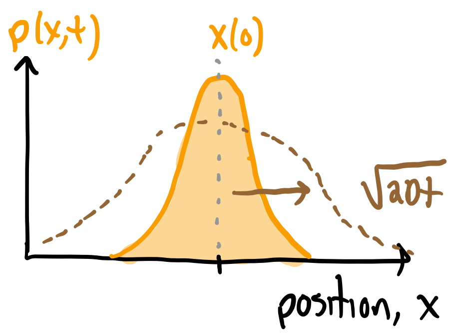
⇒ Some other measured values:

1. sugar in H_2O: $D \approx (20\,\mu m)^2/s$
2. ATP in intracellular fluid: $D \sim (10\,\mu m)^2/s$
3. protein in intracellular fluid: $D \sim (3\,\mu m)^2/s$

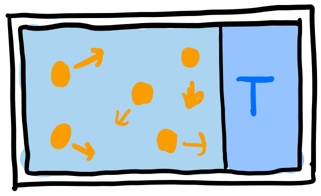
Upshot: Probability distribution for position of single particle



$$p(x,t) = \frac{1}{\sqrt{4\pi D t}}\, e^{-\frac{(x-x(0))^2}{4Dt}}$$



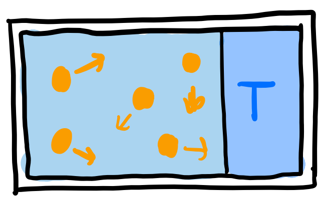
⇒ concentration field $c(x,t)$ for N solute particles:



$$c(x,t) = \sum_{i=1}^{N} \frac{1}{\sqrt{4\pi D t}} e^{-\frac{(x-x_i(0))^2}{4Dt}} = \int \frac{dx_0}{\sqrt{4\pi D t}} e^{-\frac{(x-x_0)^2}{4Dt}} c(x_0,0)$$

⇒ solution to differential equation:

$$\frac{\partial c(x,t)}{\partial t} = D \frac{\partial^2 c(x,t)}{\partial x^2}$$

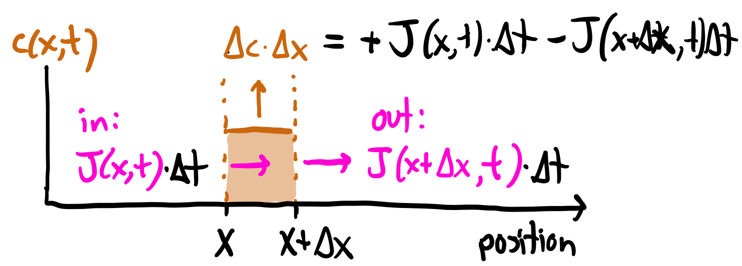


the "diffusion equation" ⇒ describes temporal dynamics of particles in solution

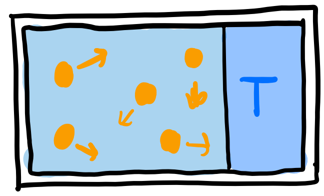
⇒ useful to rewrite in terms of particle flux, $J(x,t)$

$$\frac{\partial c(x,t)}{\partial t} = -\frac{\partial J(x,t)}{\partial x}$$

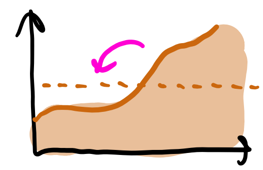
(conservation of mass)



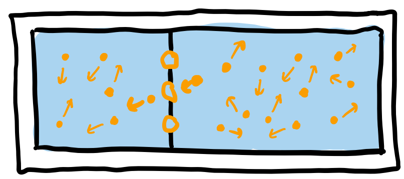
Flux from diffusion: $J_d(x,t) = -D\,\dfrac{\partial c(x,t)}{\partial x}$



"Fick's law" $\Rightarrow$ diffusion flows <u>down</u> concentration gradients

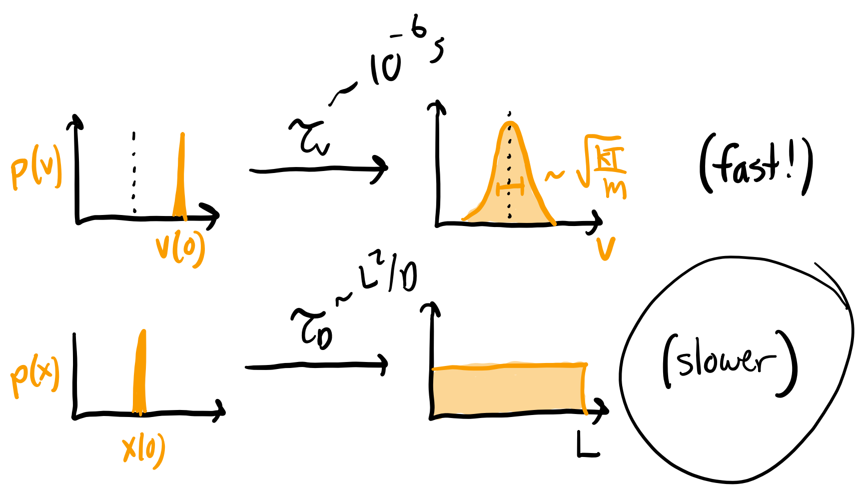


$\Rightarrow$ stops when concentrations equalize (as expected from thermal eq.)



$\Rightarrow$ diffusion = mechanism for approaching thermal eq.

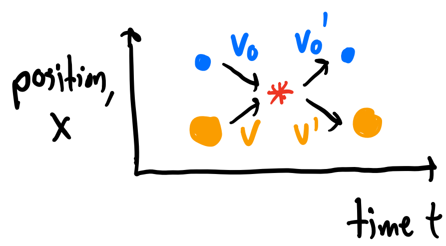
<u>2 important timescales:</u>



next time.

Supplemental Note 1: Change in velocity after a collision

In our simple elastic collision problem, the total energy & momentum of the system are conserved:



conservation of momentum: $mv + m_0 v_0 = mv' + m_0 v_0'$

conservation of energy: $\frac{1}{2}mv^2 + \frac{1}{2}m_0 v_0^2 = \frac{1}{2}mv'^2 + \frac{1}{2}m_0 v_0'^2$

$\Rightarrow$ solving for v_0 in the first eq. & plugging into second:

$$mv^2 + m_0 v_0^2 = mv'^2 + m_0\left[v_0 + \frac{m}{m_0}(v-v')\right]^2$$

$$\Rightarrow \cancel{(v-v')}(v+v') = 2\cancel{(v-v')}v_0 + \frac{m}{m_0}(v-v')^{\cancel{2}}$$

$$\Rightarrow v' = \left[1 - \frac{2m_0}{m_0+m}\right]v + \underbrace{\frac{2m_0}{m_0+m}}_{} \cdot v_0$$

$\approx \frac{2m_0}{m}$ when $m_0 \ll m$ ✓

Supplemental Note 2: Summing geometric series for $\langle x(t)^2 \rangle$

$$\langle [x(b) - x(0)]^2 \rangle = \Delta t_c^2 \sum_{b=0}^{t/\Delta t_c - 1} \sum_{b'=0}^{t/\Delta t_c - 1} \left(1 - \frac{\gamma \Delta t_c}{m}\right)^{|b-b'|} \langle v^2 \rangle$$

$$= \Delta t_c^2 \langle v^2 \rangle \left[\sum_{b=0}^{t/\Delta t_c - 1} 1 + 2 \sum_{b=0}^{t/\Delta t_c - 1} \sum_{b'=0}^{b-1} \left(1 - \frac{\gamma \Delta t_c}{m}\right)^{(b-b')} \right]$$

$$= \Delta t_c^2 \langle v^2 \rangle \left[\frac{t}{\Delta t_c} + 2 \sum_{b=0}^{t/\Delta t_c - 1} \left(1 - \frac{\gamma \Delta t_c}{m}\right)^b \cdot \frac{1 - \left(\frac{1}{1 - \frac{\gamma \Delta t_c}{m}}\right)^b}{1 - \frac{1}{\left(1 - \frac{\gamma \Delta t_c}{m}\right)}} \right]$$

$$= \Delta t_c^2 \langle v^2 \rangle \left[\frac{t}{\Delta t_c} + \frac{2\left(1 - \frac{\gamma \Delta t_c}{m}\right)}{\frac{\gamma \Delta t_c}{m}} \sum_{b=0}^{t/\Delta t_c - 1} \left[1 - \left(1 - \frac{\gamma \Delta t_c}{m}\right)^b \right] \right]$$

$$= \Delta t_c^2 \langle v^2 \rangle \left\{ \frac{2\left(1 + \gamma \Delta t_c\right)}{\frac{\gamma \Delta t_c}{m}} \cdot \frac{t}{\Delta t_c} + \frac{2\left(1 - \frac{\gamma \Delta t_c}{m}\right)}{\left(\frac{\gamma \Delta t_c}{m}\right)^2} \left[1 - \left(1 - \frac{\gamma \Delta t_c}{m}\right)^{t/\Delta t_c} \right] \right\}$$

$$\approx \frac{2m}{\gamma} \langle v^2 \rangle \cdot t \quad \text{when} \quad \frac{\gamma \Delta t_c}{m} \ll 1, \quad t \gg m/\gamma \quad \checkmark$$