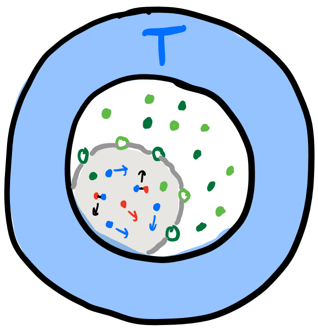
Announcements:

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

2. Solutions for practice problems 1 & 2 posted

3. Practice problems 3 posted (Lectures 4 & 5)

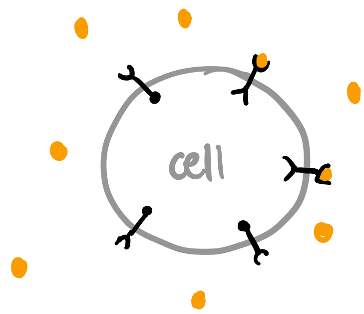
Last time: Applications of Equilibrium Statmech



$\Leftarrow$ 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?

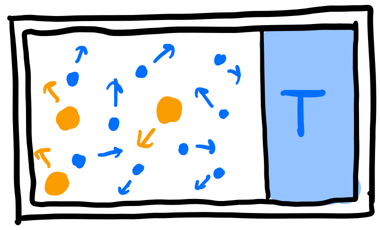
* Equilibrium statmech useful for predicting long-term states

$\Rightarrow$ 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 (e.g. ligands, cells, ...) floating around in solvent (e.g. H_2O)



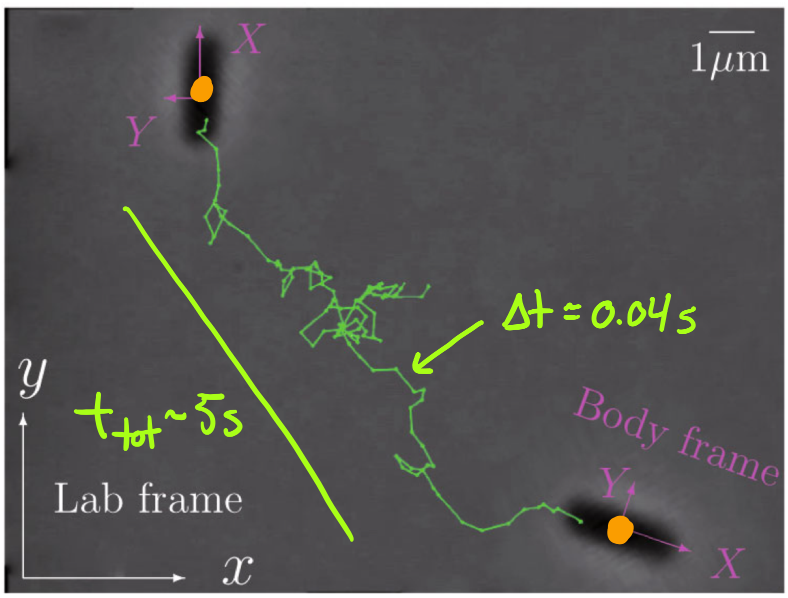
⇒ @ long times, know that system will reach thermal equilibrium

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

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

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

"Brownian motion"

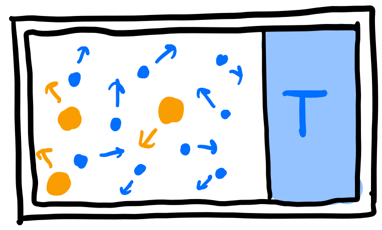


E.g. dead E.coli cell in H_2O
[Tavaddod et al 2010]

⇒ 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



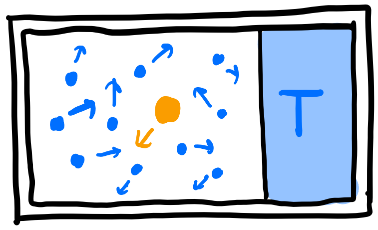
Next time: applications to sensing + cellular transport

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:

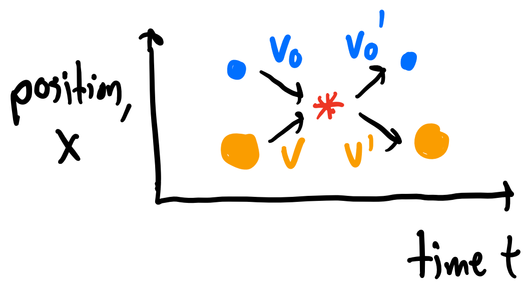


① Solute (●) = N=1 ideal particle w/ mass m

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

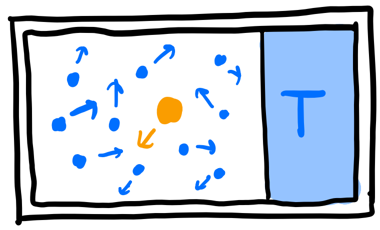
$\Rightarrow$ has <u>exact</u> <u>solution</u> as <u>sum</u> over $v_0(n)$:

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

$\leftarrow$ sum over collisions

"discount factor"

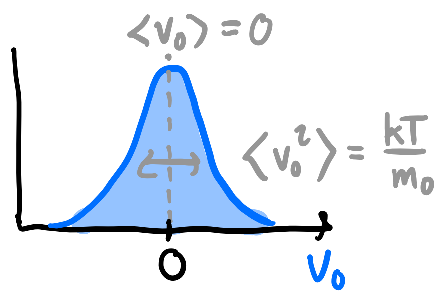
$\Rightarrow$ answer will depend on specific sequence of $v_0(1), v_0(2), \ldots$



<u>Key</u> <u>insight</u>: model these as <u>statistical</u> <u>distribution</u> of independent random variables

① $v_0(n)$ are drawn from <u>Boltzmann dist'n</u> for solvent:

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



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

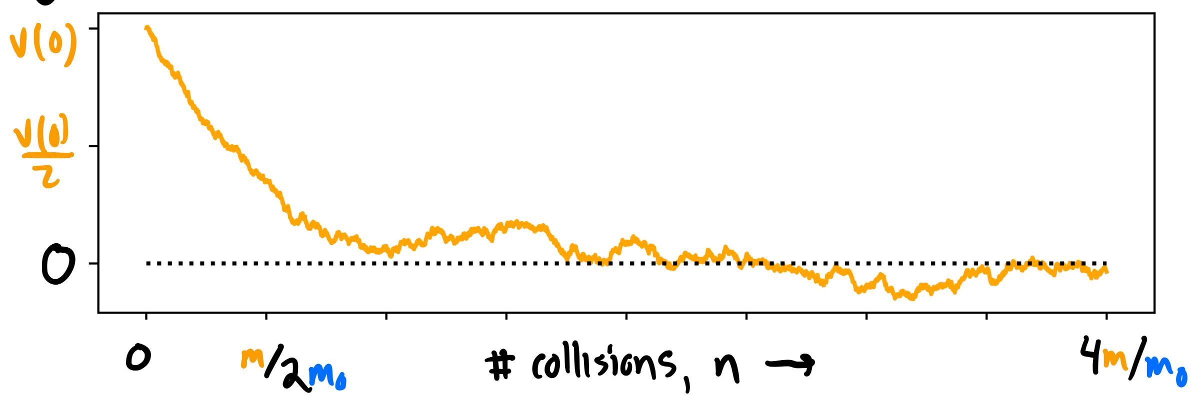
$+$ <u>variance</u> $\langle v_0^2 \rangle = \frac{kT}{m_0}$

② Times between collisions are <u>independent</u> of $v(n)$

and have mean $\langle \tau(n) \rangle = \bar{\tau}$

time between $n-1^{th}$ & n^{th} collision

E.g an example trajectory for $v(n)$ (see attached code)



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 $n_c \ll m/m_0$)

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

$\Rightarrow$ why "drag"?

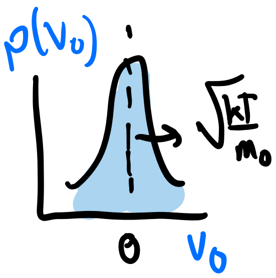
$\Rightarrow$ Normally, $F_{drag} = -\gamma \cdot v \iff \Delta v_{drag} = \frac{F_{drag}}{m}\cdot \Delta t = -\frac{\gamma}{m} v \Delta t$

$\Rightarrow$ 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/



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

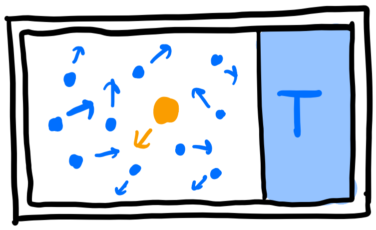
and $\quad \langle \Delta V_{random}^2 \rangle = \left(\frac{2m_0}{m}\right)^2 \sum_{n=1}^{\Delta t_b/\tau} \langle \cancel{v_0(n)^2}^{\;kT/m_0} \rangle = \left(\frac{2m_0}{m}\right)^{\cancel{2}} \frac{\Delta t_b}{\tau} \times \frac{kT}{\cancel{m_0}}$

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

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

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

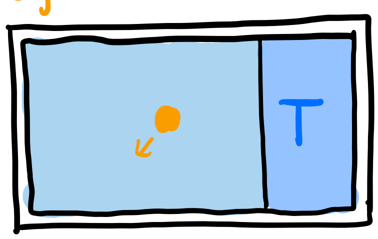
$\Rightarrow$ depends on solvent only through drag coefficient γ!



$\Rightarrow$ **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 : $a \sim 10^{-6}\,m = 1\,\mu m$



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

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

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

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

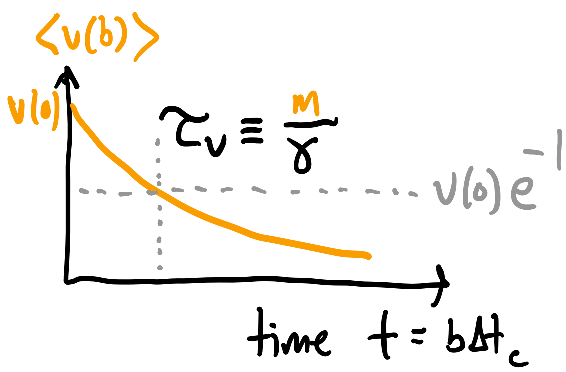
$\Rightarrow$ total time $t = b\cdot\Delta t_b$

$\Rightarrow$ Can we understand this behavior?

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

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

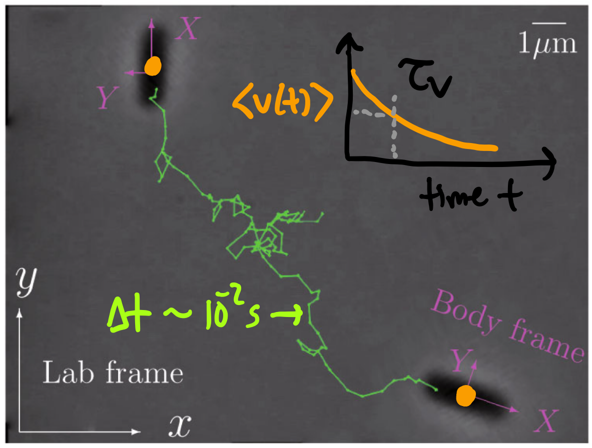
$$\approx e^{-\frac{\gamma t}{m}}\cdot v(0)$$



$\Rightarrow$ drag eliminates avg velocity

on timescale: $\tau_v \equiv \frac{m}{\gamma} = \frac{1}{6\pi\eta}\left(\frac{\overset{a^3}{m}}{a}\right)$ ***

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



$$\tau_v \approx \frac{1}{\cancel{6\pi}\ 20 \left(10^{-3} \frac{N \cdot s}{m^2}\right)} \times \left(\frac{10^{-15}\ kg}{10^{-6}\ m}\right)$$

$$\approx \frac{10^{-15}}{10^{-8}} = 10^{-7} s$$

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

Variance:

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

Fact: for independent random variables, variance of sum = sum of variances

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

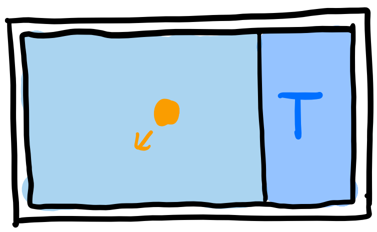
(supplemental notes)

$$\langle v(b)^2\rangle = \frac{\cancel{m}}{2\cancel{\gamma}\cancel{\Delta t_b}}\cdot\overbrace{\left\langle \Delta v_{random}^2\right\rangle}^{2\frac{\cancel{\gamma}}{\cancel{m}}\cancel{\Delta t_b}\frac{kT}{\cancel{m}}}\cdot\left[1-\cancel{e^{-\frac{2\gamma}{m}t}}\right] \quad t \gg \tau_v$$

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

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

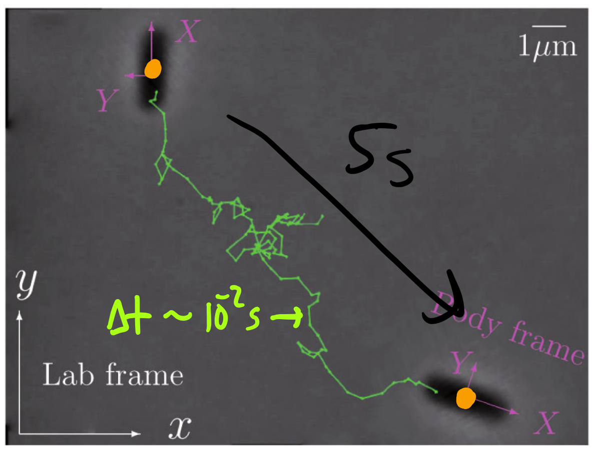
As expected in thermal equilibrium for solute (●)



$\Rightarrow$ for E.coli in H_2O:

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

$$\sim 2000\ \mu\text{m/s} \ !$$



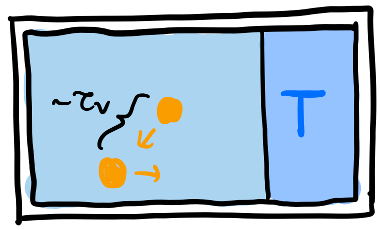
Catch: doesn't stay @ this same velocity for long!

Can calculate how long by looking @ <u>correlations</u> over time:

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

$$\approx e^{-\frac{\gamma t}{m}} = e^{-\frac{t}{\tau_v}}$$

$\Rightarrow$ "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: $\Delta x_v \sim (10^3\ \mu m/s)\cdot(10^{-7} s) \sim 10^{-4}\ \mu m$

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

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

<u>correlated</u> Gaussians w/ mean + covariance calculated above

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

$$\text{mean } \langle x(t)\rangle = x(0) + \sum_{b=0} \Delta t_b \underbrace{\cancel{\langle v(b)\rangle}}^{0} = x(0)$$

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

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

use correlation result.

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

(supplemental note)

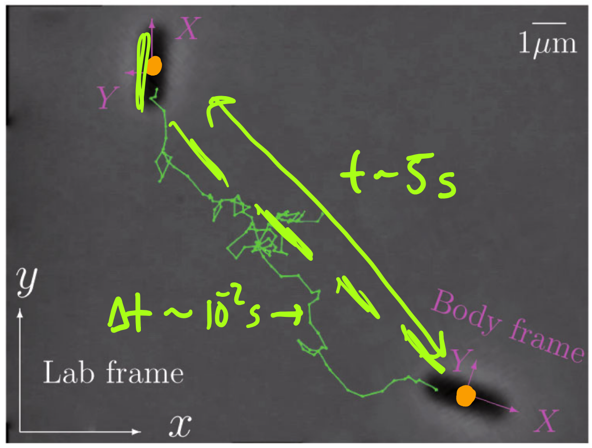
$$\Rightarrow \langle \Delta x^2\rangle \approx \cancel{\Delta t_b^2}\cdot \frac{t}{\cancel{\Delta t_b}}\cdot \frac{2\cancel{m}}{\gamma\cancel{\Delta t_b}}\cdot \underbrace{\cancel{\langle v^2\rangle}}_{kT/\cancel{m}} = 2\underbrace{\frac{kT}{\gamma}}_{=\text{ diffusion constant, } D}\times t$$

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

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

*** "Stokes–Einstein relation"

E.g. E. coli in H_2O:



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

$$\simeq 0.2\frac{(\mu m)^2}{s}$$

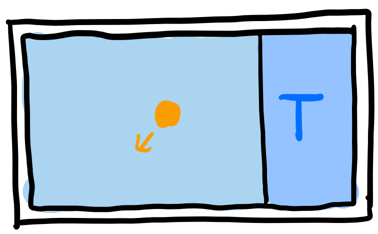
$$\sqrt{\langle \Delta x^2\rangle} = \sqrt{2\times 0.2\frac{\mu m^2}{s}\times 5s} = \sqrt{2}\ \mu m = 1\text{-}2\mu m$$

$\Rightarrow$ Some other measured values:

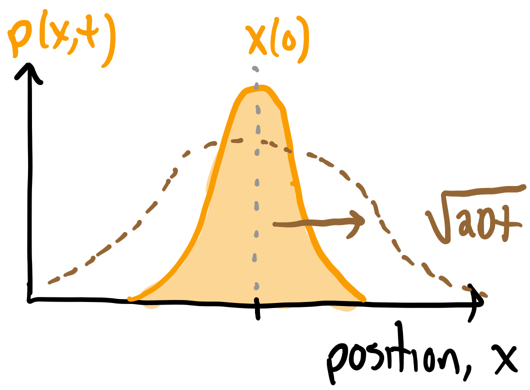
$= 400\ \mu m^2/s$

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

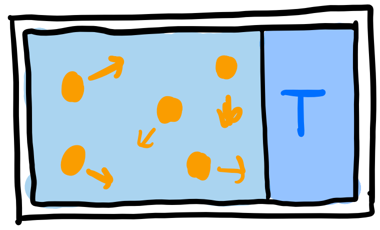
Upshot: Probability distribution for position of single particle



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



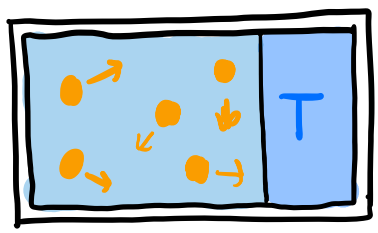
⇒ concentration field $c(x,t)$
for N solute particles:



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

⇒ solution to differential equation:

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



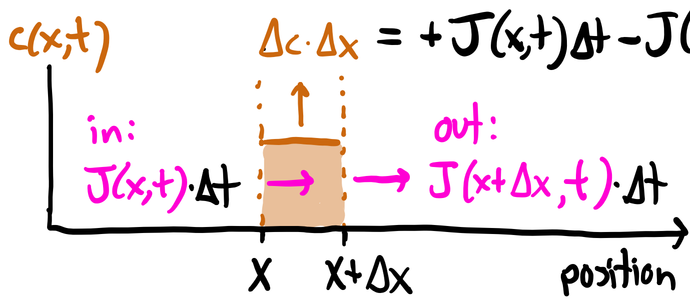
the "diffusion equation" ⇒ describes temporal dynamics of particles in solution

⇒ 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)

$$\Delta c \cdot \Delta x = +J(x,t)\Delta t - J(x+\Delta t)\Delta t$$



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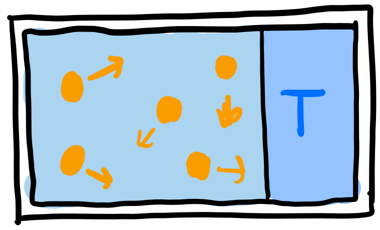
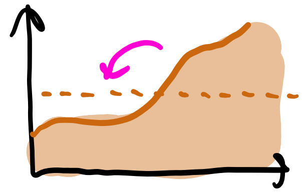
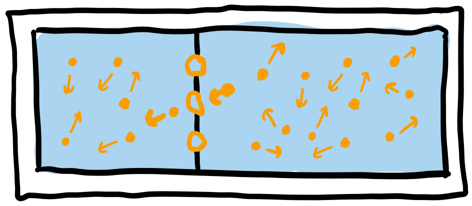
Flux from diffusion: $J_d(x,t) = -D \dfrac{\partial c(x,t)}{\partial x}$



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

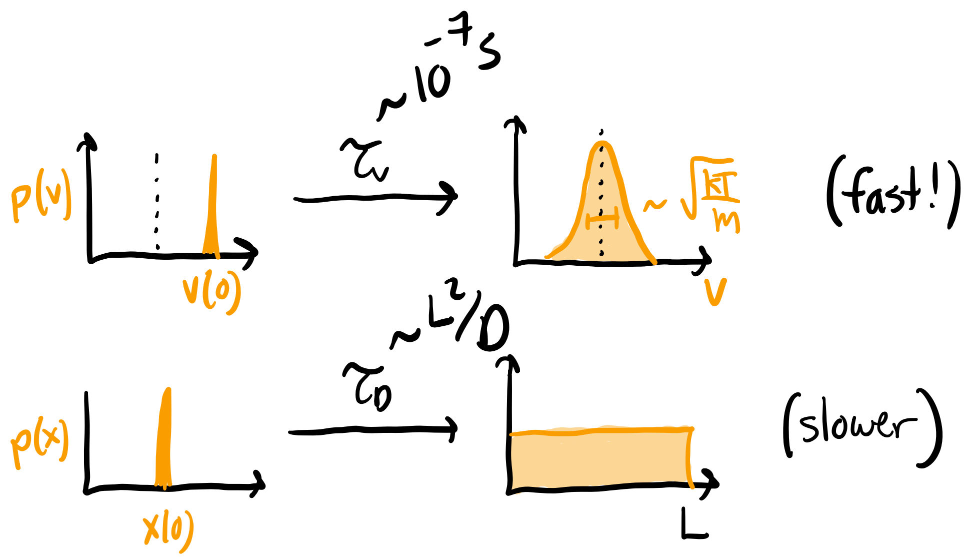


$\Rightarrow$ stops when concentrations equalize (as expected from thermal eq.)



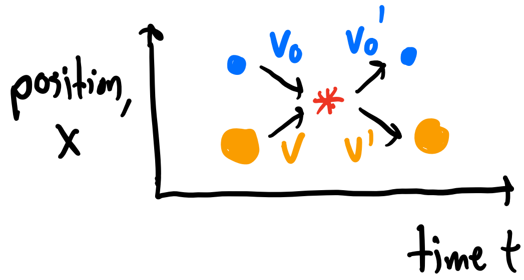
$\Rightarrow$ diffusion = mechanism for approaching thermal eq.

<u>2 important timescales:</u>



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 $\langle x(t)^2 \rangle$

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

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

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

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

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

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