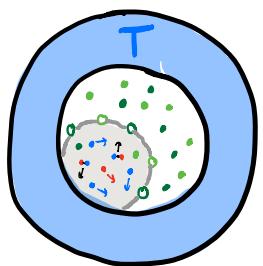
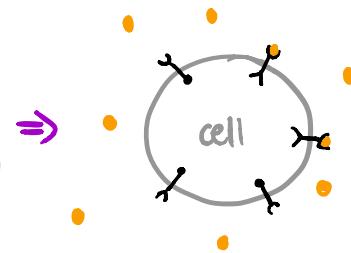


Last time: Applications of Equilibrium Statmech



Boltzmann dist'n
 $p(\vec{s}) \propto e^{-E(\vec{s}) + \mu N(\vec{s}) / kT}$



① How do cells build costly molecules?

② How do cells measure their environment?

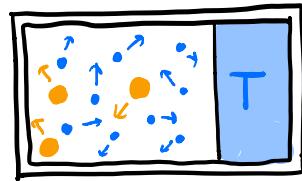
* Equilibrium statmech useful for predicting long-term states

\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. H₂O)



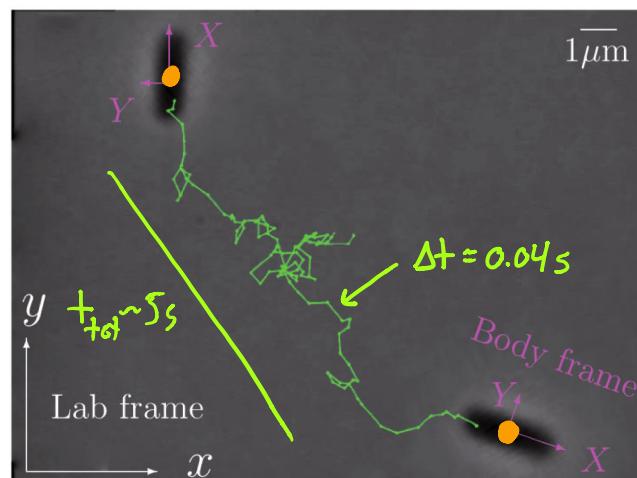
⇒ @ long times, know that system will reach thermal equilibrium

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

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

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

"Brownian motion"

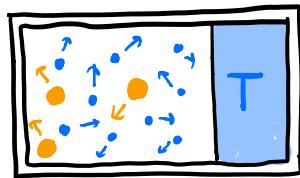


E.g. dead E.coli cell in H₂O
[Tavaddod et al 2010]

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

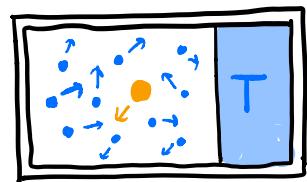
\Rightarrow imposes strong constraints on biology

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



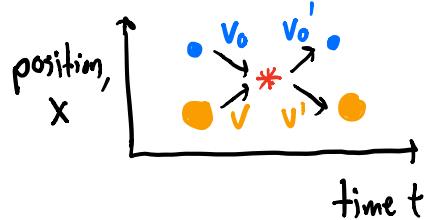
Tuesday: applications to sensing + cellular transport

Let's start w/ simple model:



- ① Solute (●) = $N=1$ ideal particle w/ mass m
- ② Solvent (•) = $N \gg 1$ ideal particles w/ mass $m_s \ll m$
- ③ Elastic collisions between ● + •'s

\Rightarrow for simplicity,
start w/ 1D



\Rightarrow simple problem in classical mechanics :

$$v' = \left(1 - \frac{2m_s}{m}\right)v + \frac{2m_s}{m}v_0 \quad (\text{supplemental note})$$

\Rightarrow recursion relation for ● velocity after n collisions :

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

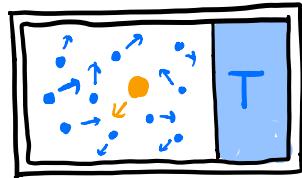
\swarrow velocity of
solute particle
in n^{th} collision

\nwarrow velocity right after n^{th} collision

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

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

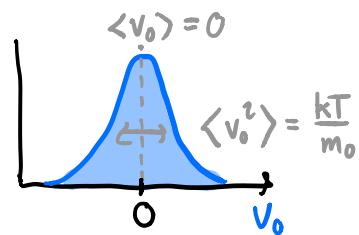
\Rightarrow answer will depend on
specific sequence of $v_o(1), v_o(2), \dots$



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

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

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



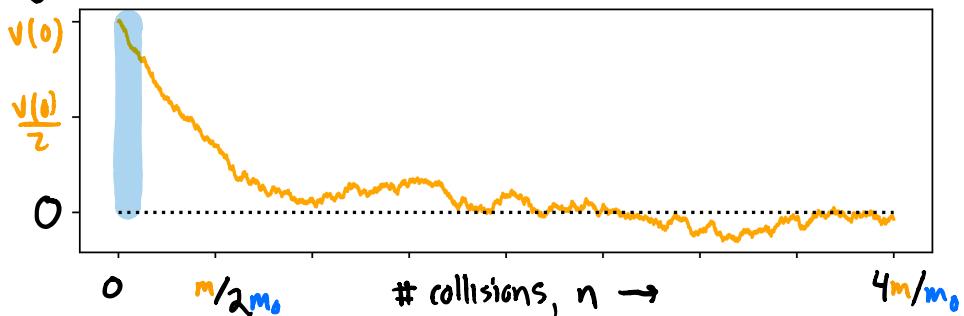
\Rightarrow Gaussian distribution w/ mean $\langle v_o \rangle = 0$

$$+ \text{ variance } \langle v_o^2 \rangle = \frac{kT}{m_0}$$

② Times between collisions are independent of $v(n)$

and have mean $\langle \tau(n) \rangle = \bar{\tau}$ 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 $\Rightarrow \Delta t_c \approx n_c \bar{\tau}$

\Rightarrow within a block, 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

$$\Delta v = -\frac{1}{m} \left(\frac{2m_0}{\bar{c}} \right) \cdot v \cdot \Delta t_c + \frac{2m_0}{m} \sum_{n=1}^{\Delta t_c / \bar{c}} v_o(n)$$

Δv_{drag} Δv_{random}

\Rightarrow why "drag"?

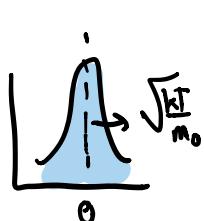
$$\Rightarrow \text{Normally, } F_{\text{drag}} = -\gamma \cdot v \Leftrightarrow \Delta v_{\text{drag}} = -\frac{\gamma}{m} v \Delta t$$

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

$$\Rightarrow \text{What about } \Delta v_{\text{random}} = \frac{2m_0}{m} \sum_{n=1}^{\Delta t / \bar{c}} v_o(n) ?$$

\Rightarrow from properties of Gaussian distribution

Δv_{random} will also be Gaussian w/



$$\langle \Delta v_{\text{random}} \rangle = \frac{2m_0}{m} \sum_{n=1}^{\Delta t / \bar{c}} \langle v_o(n) \rangle = 0$$

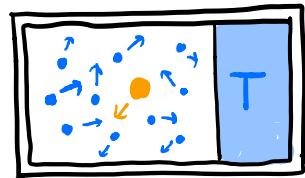
and $\langle \Delta V_{\text{random}}^2 \rangle = \left(\frac{2m_0}{m}\right)^2 \sum_{n=1}^{\Delta t_c/\bar{z}} \langle V_0(n)^2 \rangle = \left(\frac{2m_0}{m}\right)^2 \cdot \frac{\Delta t_c}{\bar{z}} \cdot \frac{kT}{m_0}$

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

\Rightarrow change in velocity across successive blocks (Δt_c)

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

\Rightarrow depends on solvent only
through drag coefficient γ !



\Rightarrow coarse-grained version holds for many other models
as long as we can predict γ !

E.g. spherical object in liquid:

Stokes Law: $\gamma = 6\pi\eta a$ ← radius

↑ Viscosity

e.g. E. coli: $10^{-6} \text{ m} = 1 \mu\text{m}$



[water $\sim 10^{-3} \frac{\text{N}}{\text{m}^2 \cdot \text{s}}$]

\Rightarrow solution after many blocks (Δt_c) is given by:

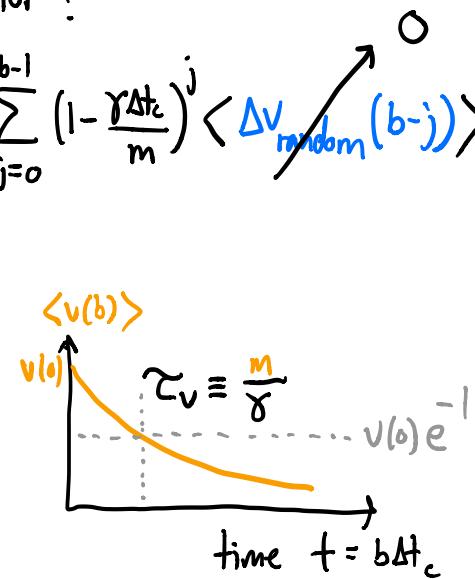
$$v(b) = \left(1 - \frac{r\Delta t_c}{m}\right)^b v(0) + \sum_{j=0}^{b-1} \left(1 - \frac{r\Delta t_c}{m}\right)^j \Delta v_{\text{random}}(b-j)$$

$$\omega / + = b \Delta t_c$$

\Rightarrow Can we understand this behavior?

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

$$\begin{aligned} \langle v(t) \rangle &= \left(1 - \frac{r\Delta t_c}{m}\right)^{t/\Delta t_c} v(0) \\ &\approx e^{-\frac{rt}{m}} \cdot v(0) \end{aligned}$$



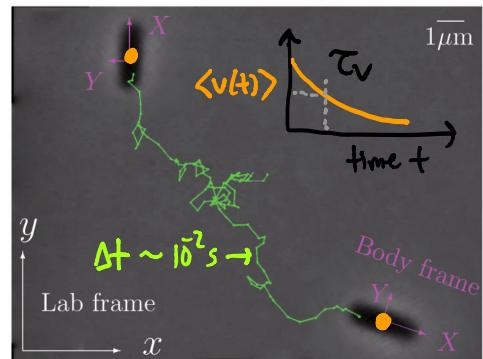
\Rightarrow drag eliminates avg velocity

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

\Rightarrow e.g. for E.coli in H₂O

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

$$\sim 10^{-6} \text{ s}$$



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

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

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



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

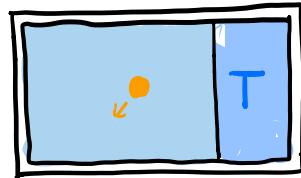
$$= \sum_{j=0}^{b-1} \left(1 - \frac{\gamma \Delta t_c}{m}\right)^{2j} \langle \Delta v_{\text{random}}^2 \rangle \quad \leftarrow \text{geometric series.}$$

$$\langle v(b)^2 \rangle = \frac{m}{2\gamma \Delta t_c} \cdot \underbrace{\langle \Delta v_{\text{random}}^2 \rangle}_{2 \frac{\sigma}{m} \Delta t_c \frac{kT}{m}} \cdot \left[1 - e^{-\frac{2\sigma}{m} + \frac{\Delta t_c}{\tau_v}} \right]$$

0 when
 $\Delta t_c \gg \frac{m}{\sigma}$

$$\Rightarrow \langle v(b)^2 \rangle \approx \frac{kT}{m} \quad \text{when } \Delta t_c \gg \tau_v = \frac{m}{\sigma}$$

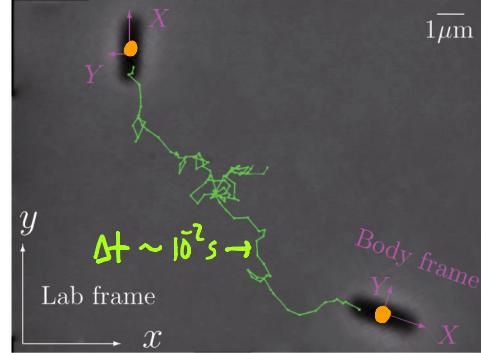
As expected in thermal equilibrium for solute (●)



\Rightarrow for E.coli in H₂O :

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

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

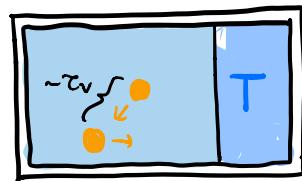


Catch: doesn't stay @ this same velocity for long!

\Rightarrow Can calculate correlations over time:

$$\frac{\langle v(b+j)v(b) \rangle}{\langle v(b^2) \rangle} = \frac{\langle (1 - \frac{r\Delta t}{m})^j v(b) \cdot v(b) \rangle}{\langle v(b)^2 \rangle} = (1 - \frac{r\Delta t}{m})^j \approx e^{-\frac{r}{m} \cdot (\Delta t \cdot j)}$$

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



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

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

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

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

correlated Gaussians
w/ mean & covariance
calculated above

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

$$\text{mean } \langle x(t) \rangle = x(0) + \sum_b \Delta t_c \langle y(b) \rangle^{10} = x(0)$$

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

$$= \Delta t_c^2 \sum_{b,b'}^{+/\Delta t_c-1} \langle v(b)v(b') \rangle$$

$$= \Delta t_c^2 \sum_{b,b'}^{+/\Delta t_c-1} \left(1 - \frac{\gamma \Delta t_c}{m} |b-b'| \right) \langle v(b)^2 \rangle$$

↙ (supplemental note)

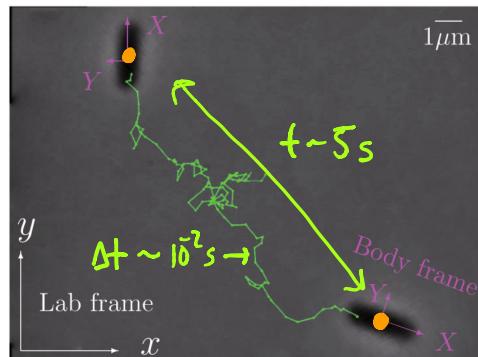
$$\Rightarrow \langle \Delta x^2 \rangle \approx \Delta t_c^2 \cdot \frac{1}{\Delta t_c} \cdot \frac{2m}{\gamma \Delta t_c} \cdot \langle v^2 \rangle = 2 \cdot \underbrace{\frac{kT}{\gamma}}_D \cdot f \equiv 0$$

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

$$\Rightarrow \underline{\text{Diffusion coefficient}}: D = \frac{kT}{\gamma} = \frac{kT}{6\pi\eta a} \quad \text{"Einstein relation"}$$

E.g. E.coli in H_2O :

$$2D = \frac{2 \cdot (4 \times 10^{21} J)}{(10^{-2} \frac{m^2}{s}) \cdot (1 \mu m)} \sim 1 \frac{Nm^2}{s}$$



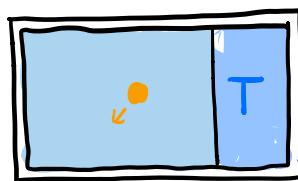
⇒ Some other measured values:

① sugar in H_2O : $D \approx (20 \mu m)^2/s$

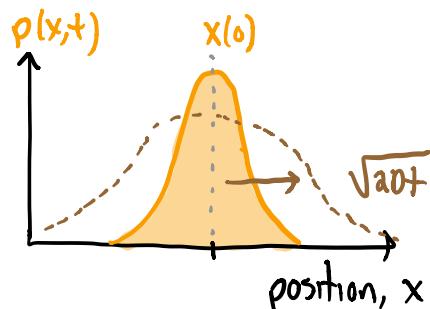
② ATP in intracellular fluid: $D \sim (10 \mu m)^2/s$

③ protein in intracellular fluid: $D \sim (3 \mu m)^2/s$

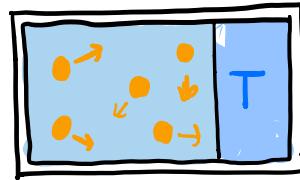
⇒ Probability distribution for position of single particle:



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



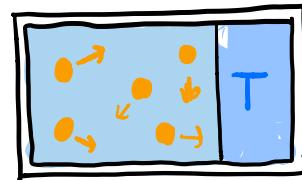
\Rightarrow concentration field $c(x,t)$
for N solute particles:



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

\Rightarrow solution to differential equation:

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

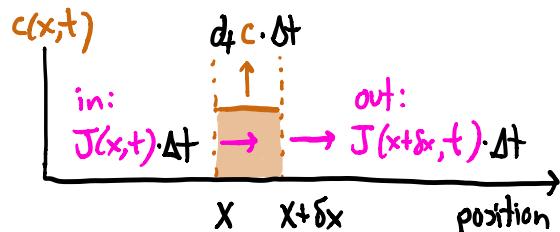


the "diffusion equation"

\Rightarrow describes temporal dynamics of particles in solution

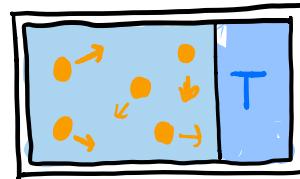
\Rightarrow useful to rewrite in terms of particle flux, $J(x,t)$

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



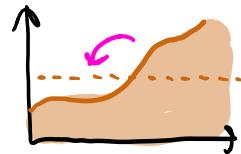
Flux from diffusion:

$$J_d(x,t) = -D \frac{dc(x,t)}{dx}$$

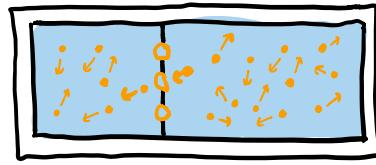


"Fick's law"

\Rightarrow diffusion flows down concentration gradients

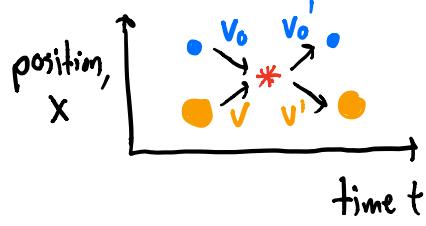


\Rightarrow stops when concentrations equalize
(as expected from thermal eq.)



Supplemental Note 1: Change in velocity after a collision

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



$$\text{conservation of momentum: } m v + m_0 v_0 = m v' + m_0 v'_0$$

$$\text{conservation of energy: } \frac{1}{2} m v^2 + \frac{1}{2} m_0 v_0^2 = \frac{1}{2} m v'^2 + \frac{1}{2} m_0 v'_0^2$$

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

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

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

$$\Rightarrow v' = \left[1 - \frac{2m_0}{m_0 + m} \right] v + \underbrace{\frac{2m_0}{m_0 + m} \cdot v_0}_{\approx \frac{2m_0}{m} \text{ when } m_0 \ll m} \quad \checkmark$$

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

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

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

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

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

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

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