Physical Principles

Mechanical Forces.

Order of magnitude of forces acting on molecules.

$F = ma$ $\quad$ $1\,\text{Newton} = 1\,\text{kg}\cdot\text{m/s}^2$

Recall 1 Newton ~ the weight of 100 grams.

$\text{pN} = 10^{-12}\,\text{N}$

~ the weight of one red blood cell.

~ the optical pressure exerted by a laser pt on a screen.

Elastic	$1-10^{2}$ pN
Covalent	10^{4} pN
Viscous	$1-10^{3}$ pN
Collisional	$10^{-12} - 10^{-9}$ pN for 1 collision/s
Thermal	$10^{2}-10^{3}$ pN
Gravity	10^{-9} pN
Centrifugal	$< 10^{-3}$ pN
Electrostatic & Van der Waals	$1-10^{3}$ pN
Magnetic	$\ll 10^{-6}$ pN

$$F = \kappa x$$

Motor protein: the stiffness of the spring $\sim 1\,\mathrm{mN/m} = 1\,\mathrm{pN/nm}$

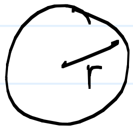
max $x \sim 10^{-9}\,\mathrm{m} \sim \mathrm{nm}$ $\therefore F \sim 1\,\mathrm{pN}$.
for protein

Viscous force: viscous force $F = \gamma v$

drag coefficient

relative velocity

Stokes law: $\gamma = 6\pi\eta r$



molecular mass of 100kDa:

$m = 166 \times 10^{-24}\,\mathrm{kg}$

$= \text{Mass of 1 mole} / N_A$

a globular protein $r \sim 3\,\mathrm{nm}$, η – viscosity

mass $\sim 100\,\mathrm{kDa}$ $\Big\} \Rightarrow \gamma \sim 60\,\mathrm{pN{\cdot}s/m}$

at 20°C
in Water.

thermal speed $\sim 8\,\mathrm{m/s}$

$\Longrightarrow$ viscous force $\sim \left(60\,\mathrm{pN{\cdot}s/m}\right)\cdot\left(8\,\mathrm{m/s}\right)$

$\sim 480\,\mathrm{pN}$

E. Coli length $2\,\mu\mathrm{m}$

$v \sim 25\,\mu\mathrm{m/s}$

$\therefore f \gtrsim \gamma v = 20\,\mathrm{n}\frac{\mathrm{N{\cdot}s}}{\mathrm{m}} \cdot 25\frac{\mu\mathrm{m}}{\mathrm{s}}$

$\sim 0.5\,\mathrm{pN}$ → The motor has to generate at least 0.5pN.

Collision & Thermal forces:

H_2O: $\sim 30 \times 10^{-27}\,\mathrm{kg}$

$v \sim 600\,\mathrm{m/s}$

$$F = \frac{d\,mv}{dt}$$

$\therefore$ momentum $\simeq mv \sim 18 \times 10^{-24}\,\mathrm{kg\,m/s}$

head on collision / second $\Longrightarrow 2 \times 18 \times 10^{-24}\,\mathrm{kg\,m/s}$

$= 36 \times 10^{-12}\,\mathrm{pN}$

But, multiple collisions (thermal force) on a 100kDa protein $\sim 500\,\mathrm{pN} \sim F_{\text{viscous}}$.

Optical Forces: The momentum of a photon: $\frac{\overset{\text{Planck's constant}}{h}\;\overset{\text{frequency of the light}}{\nu}}{\underset{\text{speed of light}}{c}}$

$$\frac{h\nu}{c} = \frac{h}{n\lambda}$$

n └ the refractive index

λ: the wavelength in vacuum.

$n_{H_2O} = 1.33$

$\lambda = 500\,nm$ (green light) } every second absorbing one such a photon ⇒ $\frac{6.6\times10^{-34}\,Js}{1.33\times500\times10^{-9}}$

the optical force $\sim 1.0\times10^{-13}\,pN$

(very small!)

Gravity: a 100 kDa protein $m \sim 166\times10^{-24}\,kg$

$mg \sim 166\times10^{-24}\,kg \cdot 9.8\,m/s^2 \sim 1.6\times10^{-9}\,pN$

— ignorable!

Centrifugal forces: ultracentrifuges ⇒ $a_c \sim 10^5 g$

100kDa protein: ⇒ $166\times10^{-18}\,N \sim 166\times10^{-6}\,pN$

⇒ Drift $\sim 3\mu m/s$

with drag coefficient

$\sim 60\,pN\,s/m$

in H_2O (20°C)

Electrostatic forces: $F = qE$ ← say, the electric field across a typical plasma membrane 15×10^{6} V/m

q: 160×10^{-21} Coulombs

↑ (6mV across the 4 nm-think membrane)

$\Rightarrow F \sim 2.4$ pN

Van der Waals: ~ 100 pN/nm^2 of protein-protein interface.

Magnetic force:

proton – the nucleus with the largest magnetic moment in the strongest NMR $\Rightarrow 10^{-12}$ pN

e.g. a huge protein of 3000 amino acids

60 000 atoms $\Rightarrow F < 10^{-6}$ pN

Terminal Velocity & Time scale of Transient.

$$m\frac{dv}{dt} + \underset{\uparrow \text{ Drag force}}{\gamma v} = \underset{\nwarrow}{F}$$

← applied force (const for now)

Sol$\underline{\text{n}}$: $v(t) = \frac{F}{\gamma}\left[1 - e^{-t/\tau}\right]$, $\tau = \frac{m}{\gamma}$

The terminal velocity: $\because \frac{dv}{dt} = 0$ as $t \to \infty$

$$\therefore v = \frac{F}{\gamma}$$

The time constant: $\tau = \frac{m}{\gamma}$ — time to reach the terminal velocity. $\gamma \nearrow$, $\tau \searrow$.

The Effects of Inertia.

Ex: How long will a bacterium continue to coast after its motors have shut and the flagella stop beating?

Suppose it swims at 25 μm/s in water.

$$m\frac{dv}{dt}+\gamma v=0 \qquad v(t)=v(0)e^{-\frac{t}{\tau}}, \qquad \tau=\frac{m}{\gamma}$$

$$m=\frac{4}{3}\pi r^3\rho \qquad r\sim 1\mu m \qquad \rho\sim 10^3\,kg/m^3$$

E. coli, the drag coefficient ~ 20 nN·s/m (Stokes law)

travelling at 25 μm/s ⇒ the motors must be able to generate $\sim 20\,nNs/m\cdot 25\,\mu m/s \sim 0.5\,pN$

$$\gamma\sim 20\,nN\cdot s/m \qquad \therefore \quad \tau=\frac{m}{\gamma}=0.2\,\mu s$$

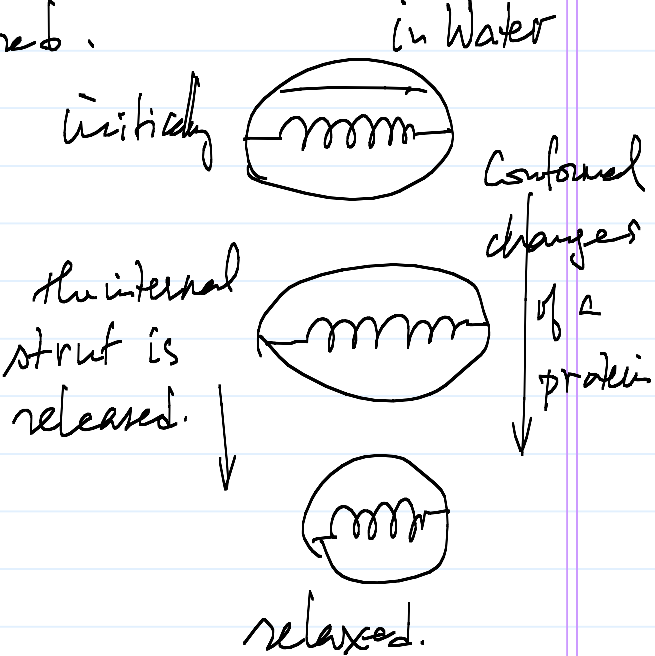
The coasting distance:

$$x=\int_0^\infty v(t)\,dt=\int_0^\infty v(0)e^{-\frac{t}{\tau}}\,d\tau = v(0)\tau = \overset{0.05\,\mathring{A}}{\overset{\shortparallel}{5\,pm}}$$

$$H_2\sim 0.5\,\mathring{A}$$

The Lesson: We can ignore the inertia effect of a bacterium.

Timescales of a Protein undergoing a global Conformational change.



∴ $\gamma \frac{dx}{dt} + \underset{\substack{\uparrow \\ \text{elastic}}}{\kappa x} = F$ — the mass is ignored.

F: applied force.

the timescale $\tau = \frac{\gamma}{\kappa}$

e.g. For a roughly globular protein,

a molecular mass ~ 100 kDa

drag coefficient $\gamma \sim 60\,\text{pN}\cdot\text{s/m}$

stiffness $\kappa \sim 4\,\text{pN/nm}$ (e.g. myosin crossbridge)

$\Rightarrow \tau \sim 15\,\text{ns}$ — much slower than the local time scales.

In contrast to the timescale of breaking the bonds between 2 proteins ~ 1 ps

Timescales involved in Chemical Bonds. (Vibration)

$m\frac{d^2x}{dt^2} + \kappa x = F \Rightarrow$ oscillations $\qquad \omega = \sqrt{\frac{\kappa}{m}}$

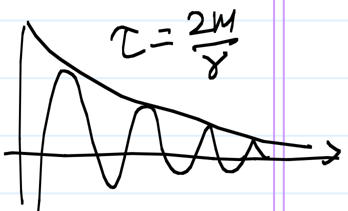
e.g. H-Cl $\qquad \nu = 89.6\times10^{12}\,\text{Hz}$ (i.e. $\lambda = \frac{c}{\nu} = \frac{0.299\times10^{9}\,\text{m/s}}{89.6\times10^{12}\,\text{Hz}}$

$m \sim 1.63\times10^{-27}\,\text{kg}$ (i.e. H mass) $\qquad = 3.53\,\mu\text{m}$ (infrared)

$\therefore \kappa = m\omega^2 = 4\pi^2\nu^2 m = 517\,\text{N/m}$

Times scales involved in a protein undergoing a large-scale conformational change in a fluid.

$$m\frac{d^2x}{dt^2} + \gamma\frac{dx}{dt} + \kappa x = F$$



$\gamma^2 < 4m\kappa$ — oscillatory (underdamped)

$\gamma^2 > 4m\kappa$ — overdamping

strongly overdamped $\Rightarrow$ $\gamma\frac{dx}{dt} + \kappa x = F$ ignoring mass.

NB: The overdamped soln

$$x(t) = \frac{F}{\kappa}\left[1 - \frac{\tau_1}{\tau_1-\tau_2}e^{-\frac{t}{\tau_1}} + \frac{\tau_2}{\tau_1-\tau_2}e^{-\frac{t}{\tau_2}}\right] \quad \text{for } x(0)=0,\ \left.\frac{dx}{dt}\right|_{t=0}=0$$

$$\tau_{1,2} = \frac{\gamma \pm \sqrt{\gamma^2 - 4m\kappa}}{2\kappa}$$

For this soln: $\underset{\substack{\uparrow \\ \text{viscous force}}}{\gamma v} - \underset{\substack{\nwarrow \\ \text{inertial force.}}}{ma} > 0 \quad \forall t.$

Overdamped motion $\Longleftrightarrow$ $\gamma v > ma$.

For Motor protein, the motor domain mass $\sim 160\times10^{-24}$ kg

$\gamma \sim 60\,\mathrm{pN\cdot s/m}$

$\kappa \sim 4\,\mathrm{pN/nm}$

$\frac{\gamma^2}{4m\kappa} \sim 1400 \gg 1$ $\Rightarrow$ its motion is highly overdamped.

$\tau \sim \frac{\gamma}{\kappa} \sim 15\,\mathrm{ns}$ $\Rightarrow$ changing to new chemical state

$\rightarrow$ no oscillations!

Thermal Forces & Diffusion

Thermal forces to Proteins and cells — from collisions with H_2O and other molecules in the surrounding fluid.

Their characteristics — the forces are proportional to temperature of the fluid particles in terms of strength.

— their directions are random ⇒ Diffusion

Why they are important? ∵ the chemical reactions that drive biological processes have energies that are only a bit higher than k_BT

⇒ thermal fluctuations are important for proteins to reach their transition states

The Boltzmann Distribution

(Recall the standard temperature 25°C is 298.15 K)

In thermal equilibrium:

$$P_i = \frac{1}{Z} e^{-\frac{U_i}{k_BT}} \qquad Z = \sum_i e^{-U_i/k_BT}$$

the absolute temperature

— partition function

↑ Boltzmann's constant $k_B = 1.38 \times 10^{-23}$ J/K

↑ The probability of finding a particle (or a system) in state i that has energy U_i (In the case of system, it is the energy of the system) at 25°C

$k_BT = 4.116 \times 10^{-21}$ J

cf. Photon ($\lambda = 500$ nm Green)

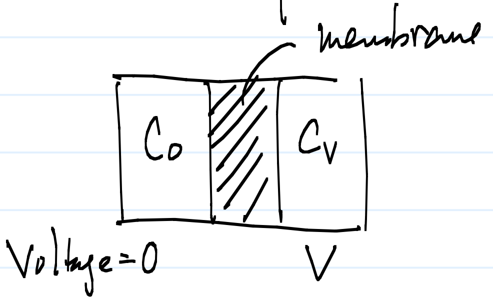
$$h\nu = \frac{hc}{\lambda} = 397 \times 10^{-21} \text{ J}$$

$$\frac{k_BT}{\Delta G_{ATP}} \sim 0.04$$

ATP hydrolysis in the

$$\Delta G = 100 \times 10^{-21} \text{ J}$$

e.g. The Nernst equation



Concentration distribution:

$$\frac{C_V}{C_0} = \frac{\rho_V}{\rho_0} = e^{-\frac{U}{k_BT}} = e^{-\frac{eV}{k_BT}}$$

— the Nernst equation

$$\frac{k_BT}{e} = \frac{RT}{F} = 25.69 \text{ mV}$$

NB: $R = N_A k_B$

Principle of Equipartition of Energy.

1.4 Equipartition Theorem

Equipartition Theorem:

If the dynamics of the system is described by the Hamiltonian:

$$H = A\zeta^2 + H'$$

where ζ is one of the general coordinates $q_1, p_1, \cdots, q_{3N}, p_{3N}$, and H' and A are independent of ζ, then

$$\left\langle A\zeta^2 \right\rangle = \frac{1}{2} k_B T$$

where $\langle\rangle$ is the thermal average, i.e., the average over the Gibbs measure $e^{-\beta H}$.

This result can be easily seen by the following calculation:

$$\begin{aligned}
\langle A\zeta \rangle &= \frac{\int A\zeta^2 e^{-\beta H} d^{3N}q d^{3N}p}{\int e^{-\beta H} d^{3N}q d^{3N}p} \\
&= \frac{\int A\zeta^2 e^{-\beta A\zeta^2} d\zeta e^{-\beta H'} [dpdq]}{\int e^{-\beta A\zeta^2} d\zeta e^{-\beta H'} [dpdq]} \\
&= \frac{\int A\zeta^2 e^{-\beta A\zeta^2} d\zeta}{\int e^{-\beta A\zeta^2} d\zeta} \\
&= -\frac{\partial}{\partial \beta} \ln \int e^{-\beta A\zeta^2} d\zeta \\
\left(x = \zeta\sqrt{\beta}\right) \qquad &= -\frac{\partial}{\partial \beta} \ln \left[\beta^{-\frac{1}{2}} \int e^{-Ax^2} dx \right] \\
&= \frac{1}{2\beta} \\
&= \frac{1}{2} k_B T
\end{aligned}$$

where $d\zeta\,[dpdq] = d^{3N}q d^{3N}p$, i.e., $[dpdq]$ stands for the phase-space volumn element without $d\zeta$.

Note that if

$$H = \sum A_i p_i^2 + \sum B_i q_i^2$$

where there are total M terms in these sums and A_i and B_i are constant, independent of $\{p_i, q_i\}$, then

$$\langle H \rangle = \left(\frac{1}{2} k_B T \right) M$$

i.e., each quadratic component of the Hamiltonian shares $\frac{1}{2} k_B T$ of the total energy. For example, the Hamiltonian for interacting gas particles is

$$H = \sum_i \frac{p_i^2}{2m} + \sum_{ij} U\left(\mathbf{r}_i - \mathbf{r}_j\right)$$

where $U\left(\mathbf{r}_i - \mathbf{r}_j\right)$ is the potential energy between any two particles. The equipartition theorem tells us that the average kinetic energy is $\frac{3}{2}k_BT$ for every particle (since there are three translational degrees of freedom for each particle). Furthermore, for an ideal gas, i.e. gas particles do not interact, we have the average total energy

$$U = \frac{3}{2}k_BTN$$

where N is the total number of particles. Then, the specific heat for this system is

$$\begin{aligned}
C_V &\equiv \left(\frac{\partial U}{\partial T}\right)_V \\
&= \frac{\partial}{\partial T}\left(\frac{3}{2}k_BTN\right) \\
&= \frac{3}{2}k_BN
\end{aligned}$$

Diffusion.

Note Title 1/20/2008

Microscopic Picture.

Diffusion — random motion of molecules or small particles due to thermal energy.

A Basic Estimate.

In thermal equilibrium:

Regardless the size of a particle:

k_B – Boltzmann's constant.

T = temperature

$$\left\langle \frac{1}{2} m v_x^2 \right\rangle = \frac{1}{2} k_B T$$

average over time in thermal equilibrium.

or over an ensemble of particles

$$\therefore \quad \sqrt{\langle v_x^2 \rangle} = \sqrt{\frac{k_B T}{m}}$$

mean square-velocity

$$v_{rms} = \sqrt{\langle v^2 \rangle} = \sqrt{\frac{3 k_B T}{m}}$$

H_2O: 640 m/s 25°C

bacterium of vol 1 μm^3

~3.5 mm/s.

e.g. Lysozyme: its molecular weight 1.4×10^4 g (for one mole)

$$\therefore \quad m = \frac{1.4 \times 10^4 \text{g}}{N_A} = \frac{1.4 \times 10^4 \text{g}}{6.0 \times 10^{23}} = 2.3 \times 10^{-20} \text{g}$$

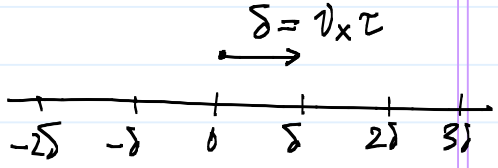
$k_B T$ (at 300°K i.e. 27°C) is 4.14×10^{-14} g cm²/sec²

$$\langle v_x^2 \rangle^{\frac{1}{2}} = 1.3 \times 10^3 \text{cm/sec}$$

But, a molecule does not travel very far due to collisions. ⇒ diffusion.

One-Dimension Random Walk.

1° a particle moves at $\pm v_x$ every τ seconds.



2° $\text{prob}(\rightarrow) = \text{prob}(\leftarrow) = \frac{1}{2}$

3° Each particle moves independently of all other particles. (i.e. particles do not interact — Dilute Limit)

assumption: v, τ Const. — they will depend on T and details of material structure.

i^{th} particle: $$x_i(n) = x_i(n-1) \pm \delta$$

Mean: $$\langle x(n)\rangle \equiv \frac{1}{N}\sum_{i=1}^{N} x_i(n)$$

NB: $$\langle x(n)\rangle = \frac{1}{N}\sum_{i=1}^{N} x_i(n-1) \pm \delta = \langle x(n-1)\rangle$$

∴ the mean position remains Constant.

Variance:

$$x_i^2(n) = x_i^2(n-1) \pm 2\delta\, x_i(n-1) + \delta^2$$

$$\therefore \quad \langle x^2(n)\rangle \equiv \frac{1}{N}\sum_{i=1}^{N} x_i^2(n) = \frac{1}{N}\sum_{i=1}^{N} x_i^2(n-1) \pm 2\delta x_i(n-1) + \delta^2$$

$$= \langle x^2(n-1)\rangle + \delta^2$$

$$\therefore \quad \langle x^2(n)\rangle = n\delta^2 \qquad \because \ t = n\tau$$

$$\therefore \quad \langle x^2(t)\rangle = \left(\frac{\delta^2}{\tau}\right) t$$

Diffusion coefficient $D = \frac{\delta^2}{2\tau}$ $\therefore$ $\langle x^2(t)\rangle = 2Dt$

or $\sqrt{\langle x^2(t)\rangle} = \sqrt{2D}\, t^{1/2}$

$\sim t^{\frac{1}{2}}$

↑ depending on

1. the size of particle,
2. the proper of the medium
3. the temperature.

e.g. For a small particle,

$D \simeq 10^{-5}\,\mathrm{cm^2/sec} = 10^{-9}\,\mathrm{m^2/s}$

$= \underline{1\,\mu\mathrm{m}^2/\mathrm{msec}}$

in water
at room temperature.
(Remember this!)

the width of a bacterium $\sim 10^{-6}$ m $\sim 1\,\mu$m

To diffuse $x \sim 1\,\mu$m

$t \sim \frac{x^2}{2D} \sim \frac{1}{2}$ msec ~ 0.5 msec.

To diffuse $x \sim 1$ cm (the width of test tube)

$t \sim \frac{x^2}{2D} = 5\times10^{4}$ sec ~ 14 hrs.

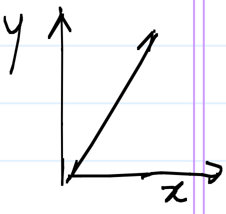
Important: It takes long time to mix using diffusion alone.

e.g. Why the diameter of eukaryotic cells are usually smaller 100 μm?
a 1μm-sized organelle (e.g. mitochondria) in water $D \sim 0.5\,\mu\mathrm{m}^2/\mathrm{s}$ (25°C)
diffuse 100 μm ~ 3hrs. (In cytoplasm, even slower)
⇒ motor proteins are needed for transport.

NB: 2D and 3D random walks

2D. $r^2 = x^2 + y^2$. $\therefore$ $\langle r^2\rangle = 4Dt$

3D: $\langle r^2\rangle = 6Dt$

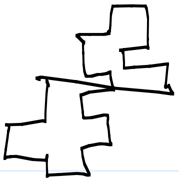


NB. Recurrent: the walker returns to its starting pt within a finite time with probability 1.

Transient: the recurrence does not occur. (i.e. with prob < 1)

2D: Random Walk is recurrent

3D: Random Walk is transient



(Why?). (2-D) The area of walker in N steps is $O((\sqrt{N})^2) = O(N)$

∵ N segments fill an area of size $\sqrt{N}$, which contains $\sim (\sqrt{N})^2 = N$ segments.

(3-D): The volume of walker in N steps is

$$(\sqrt{N})^3 \sim N^{3/2}$$

it contains $\sim N^{3/2}$ line segments

$N^{3/2} > N$ ⇒ the walker unlikely to visit the origin again.

Q What is the distribution of the walker?

∵ The location of the walker is $x = \sum_{n=1}^{N} x(n)$ (in 1D)

∴ the central limit theorem ⇒

$$x(n) = \begin{cases} +1 & \text{prob } p \\ -1 & \text{〃 } q \end{cases}$$

$p + q = 1$

the mean of $\sum x(n)$

$$z = \frac{\sum^{N} x(n) - N(p-q)}{\sigma_B \sqrt{N}}$$

$x(n)$ — the Bernoulli r.v.

σ_B — variance $2\sqrt{pq}$ for Bernoulli r.v. (NB: +1, −1 Not +1, 0

$N \gg 1$ $z \sim N(0,1)$ i.e. Gaussian distribution $\frac{1}{\sqrt{2\pi}} e^{-\frac{z^2}{2}}$

Roughly, the prob of finding the particle in $(X, X+dX)$ is

$$\frac{1}{\sqrt{2\pi}\,\sigma} e^{-\frac{(X-\mu)^2}{2\sigma^2}} dX, \qquad \mu = Np, \quad \sigma^2 = 4Npq$$

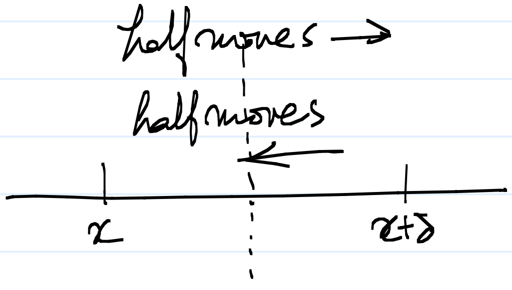
For $p = q = \frac{1}{2}$ symmetric walker, $t = N\tau$, $x = \delta \cdot X$

$$\sigma^2 = 4 \cdot \frac{t}{\tau} \cdot \frac{1}{2} \cdot \frac{1}{2} = \frac{t}{\tau} \qquad D = \frac{\delta^2}{2\tau}$$

The prob density distribution for x is $\frac{1}{\sqrt{4\pi D t}} e^{-\frac{x^2}{4Dt}}$

Macroscopic Description.

Fick's equations.



Q: How many particle will move across unit area in unit time from x to $x+\delta$?

$N(x)$

↑ # of particles at pt x at time t.

i.e. What is the net flux in the direction x?

net number crossing to the right is

$$-\frac{1}{2}\left[N(x+\delta) - N(x)\right]$$

↑ half of the particles move across the dashed line

∴ over the time interval τ

$$J_x = -\frac{1}{2}\left[N(x+\delta) - N(x)\right] / A\tau$$

$$D = \frac{\delta^2}{2\tau}$$

$$= -\frac{\delta^2}{2\tau}\cdot\frac{1}{\delta}\left(\frac{N(x+\delta)}{A\delta} - \frac{N(x)}{A\delta}\right)$$

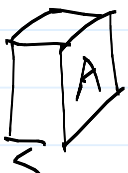
↖ the Concentration $C(x)$

$$= -D\,\frac{1}{\delta}\left[C(x+\delta) - C(x)\right]$$

$\delta \to 0$ $\quad J_x = -D\frac{\partial C}{\partial x}$ (Fick's first equation)

The Conservation of the total number of particles (locally)

In a small box:



$$\frac{1}{\tau}\left(C(t+\tau) - C(t)\right)\cdot A\delta = -\frac{1}{\tau}\left(J_x(x+\delta) - J_x(x)\right)\cdot A\tau$$

↑ # of particles increased in τ $\qquad$ ↑ the flux out, ↑ the flux in

∴ $\tau \to 0,\ \delta \to 0$ $\quad \frac{\partial C}{\partial t} = -\frac{\partial J_x}{\partial x}$

∴ $\frac{\partial}{\partial t}C = D\frac{\partial^2 C}{\partial x^2}$ — Fick's 2nd equation

— the result of Conservation Law together with the Constitutive relation

3D:

$$\begin{cases} \frac{\partial}{\partial t}C(\vec{x},t) = D\nabla^2 C(\vec{x},t) & \left(\text{Laplacian } \nabla^2 = \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2}\right) \\ \vec{J} = -D\nabla C(\vec{x},t) & (\text{isotropic assumption}) \end{cases}$$

Special soln. — the fundamental soln.

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

if all particles are concentrated at $x = x_0$ i.e

$$C(x,t) = N\delta(x - x_0)$$

one can easily verify $C(x,t) = \frac{N}{\sqrt{4Dt}} e^{-\frac{(x-x_0)^2}{4Dt}}$ fundamental soln.

is a soln of the diffusion eqn. NB: $\lim_{t\to 0^+} C(x,t) = N\delta(x-x_0)$

— Consistent with what we derived about the random walker's prob. distribution.

∴ If the initial concentration is $C(x_0)$, then

$$C(x,t) = \int_{-\infty}^{+\infty} \frac{1}{\sqrt{4Dt}} e^{-\frac{(x-x_0)^2}{4Dt}} C(x_0)\, dx_0$$

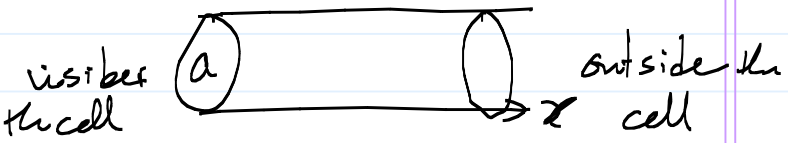
— Superposition principle for linear system.

Drift-Diffusion equations

A particle in the fluid would experience a frictional drag

$F_x = \frac{1}{\mu} v_x$ μ — mobility coefficient

Consider an ion in the channel:



Under electric field E. if the particle's charge is Ze, the electric force for the particle is $F_e = eZE$

↑ e — the elementary charge

Ze — the charge carried by the ion.

$\therefore$ $v_x = \mu \cdot ZeE$ — Drift velocity of the particle.

the corresponding electric current for ions of density $C(x)$

$i_g = v_x \cdot a Ze \cdot C(x)$

↑ crosssection of the channel

The electrical current for particles with charge Ze

$$i = \left(-D\frac{\partial c}{\partial x} + \mu ZeEC\right)\cdot aZe$$

↑ Drift under the electric field.

↑ Diffusion-induced current

From the conservation law. $\left(\frac{\partial}{\partial t} ZeC\right)a + \frac{\partial}{\partial x} i = 0$ charge conservation

$\rho = ZeC$ — charge density: $\frac{\partial \rho}{\partial t} = D\frac{\partial^2 \rho}{\partial x^2} - \mu ZeE\frac{\partial \rho}{\partial x}$.

— Drift Diffusion eqn.

The Einstein Relation: $D = k_B T \mu$

Q: Are D and μ related physically?

Under equilibrium $i = 0$

$$E = -\frac{\partial \phi}{\partial x} \qquad \phi - \text{electric potential.}$$

then $i = 0$, $$-D\frac{\partial C}{\partial x} - \mu Z e \frac{\partial \phi}{\partial x} \cdot C = 0$$

1 – outside
2 – inside

integration ⇒ $$D \log\frac{C_2}{C_1} + \mu Z e \underbrace{(\phi_1 - \phi_2)} = 0$$

$V = \phi_1 - \phi_2$ is the membrane potential

$$\therefore \quad V = \frac{D}{\mu}\cdot\frac{1}{Ze}\log\frac{C_2}{C_1} \qquad (*)$$

or $$\frac{C_1}{C_2} = e^{-\frac{eV}{(D/\mu)}}$$

From the statistical mechanics of equilibrium system we have the Boltzmann distribution i.e. the probability of finding particle in the state with energy E is

$$P_r \propto e^{-\frac{E}{k_B T}}$$

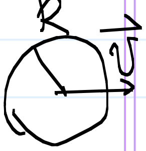
The Nernst equ.

$$\therefore \quad \frac{C_1}{C_2} = e^{-\frac{Ze\phi_1}{k_B T} - \left(-\frac{Ze\phi_2}{k_B T}\right)} = e^{-\frac{Ze}{k_B T}(\phi_1 - \phi_2)} \qquad \text{Eq(C)}$$

Comparing Eq (C) with Eq (*) $\Rightarrow$ $\frac{D}{\mu} = K_BT$

or $D = K_BT\mu$ — Einstein relation.

NB: For a particle in a stokes flow. $F_{drag} = 6\pi\overset{\text{Viscosity}}{\eta} R\cdot v$



$\therefore \mu = \frac{1}{6\pi\eta R}$. (Stokes formula)

$\therefore \eta = \frac{K_BT}{6\pi RD}$

NB: By measuring diffusion coefficient. one can obtain η.

NB: $D = K_BT\mu$ — universal.

History: Einstein's contribution: ($\Rightarrow$ Perrin & Svedberg Nobel/phys in 1926)

From $PV = N_A K_BT$ $\Rightarrow$ $N_A = \frac{K_BT}{PV}$ From $K_BT = \frac{D}{\mu}$ $\Rightarrow$ K_B, N_A

N_A — Avogadro #.

So he found how many particles in a mole,

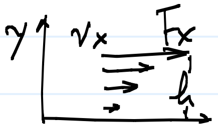
The confirmation of atomistic theory of gas & liquid.

— Measuring μ from D. in the Molecular Dynamics Simulation setting

μ is hard to measure directly for a simulated fluid.

but D is easy to compute.

NB: $F_x = \eta \frac{\partial v_x}{\partial y}\Big|_h$



— Finally the Drift-Diffusion eqn is

$$\frac{\partial C}{\partial t} = \mu\left(K_BT\frac{\partial^2 C}{\partial x^2} - Ze\frac{\partial}{\partial x}\left(\frac{\partial \phi}{\partial x}C\right)\right)$$

Examples: Diffusion of Ions.

Na^+ $\quad D_{Na^+} = 1.33\times10^{-9}\ m^2/s$ at 25°C

For $\eta = 0.89\ \underset{\uparrow 10^{-3}}{m}Pa\cdot s$, $k_BT = 4.12\times10^{-21} J$

the Einstein relation & Stokes' law ⇒

an apparent radius $\tilde{R}_{Na} = 1.8\ \text{Å}$

cf: the ionic radius measured from crystals

$R_{Na^+} \approx 0.95\ \text{Å} \sim \frac{1}{2}\tilde{R}_{Na}$

Constant-field Approximation for Ionic Current.

setup: 1° A channel with only one ion type allowed. the current is

$$I = -aZe\mu\left(k_BT\frac{\partial c}{\partial x} + Ze\frac{\partial \phi}{\partial x}c\right)$$

2° Steady state: charge cannot build up anywhere,

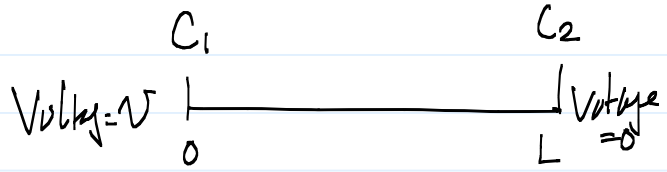
$$\therefore \quad \frac{\partial I}{\partial x} = 0$$

The Poisson eqn: $\nabla\cdot\vec{E} = \frac{\rho}{\varepsilon}$

i.e. $-\frac{\partial^2\phi}{\partial x^2} = \frac{ZeC}{\varepsilon}$

↖ the dielectric constant

3°. The boundary condition



$C(0) = C_1 \qquad C(L) = C_2$

$\phi(0) = V \qquad \phi(L) = 0$

Consider the low concentration limit.

$$C_1 = \alpha c_1, \quad C_2 = \alpha c_2 \qquad C(x) = \alpha c(x)$$

$$I = \alpha i$$

$0 < \alpha \ll 1.$

NB: We do not scale ϕ (∵ its scale is fixed by the given value V, which is not necessarily low)

After the scaling: In the limit of $\alpha \to 0$,

$$\begin{cases} i = -aZe\mu\left(k_BT\frac{\partial c}{\partial x} + Ze\frac{\partial \phi}{\partial x}c\right) & (1) \\ \frac{\partial i}{\partial x} = 0 & (2) \\ -\frac{\partial^2\phi}{\partial x^2} = 0 & (3) \end{cases}$$

with $c(0) = c_1 \quad c(L) = c_2$

$\phi(0) = V \quad \phi(L) = 0$

Eq (3) $\Rightarrow$ $\phi(x) = \frac{L-x}{L}\cdot V$

The origin of the "const-field" approximation

$$\downarrow$$

$\therefore E = -\frac{\partial\phi}{\partial x} = \frac{V}{L}$ — a constant, indep't of x

Eq (2) $\Rightarrow$ $i = i(x)$ is a const. Let $i = i_0$

$\therefore$ Eq (1) $\Rightarrow$ $c(x) = \frac{i_0 L}{a(Ze)^2\mu V} + A e^{ZeVx/k_BTL}$

integration constant

Using the boundary condition, we can determine the const i_0 and A

$$i_0 = \frac{a(Ze)^2\mu V}{L}\;\frac{c_1 e^{\frac{ZeV}{k_BT}} - c_2}{e^{ZeV/k_BT} - 1}$$

i.e. $I = \frac{a(Ze)^2\mu V}{L}\cdot\frac{c_1 e^{ZeV/k_BT} - c_2}{e^{ZeV/k_BT} - 1}$ in the original variables

NB: $I = 0$ when $C_1 e^{ZeV/k_BT} - C_2 = 0$

i.e. $V = \frac{k_BT}{Ze} \log \frac{C_2}{C_1}$

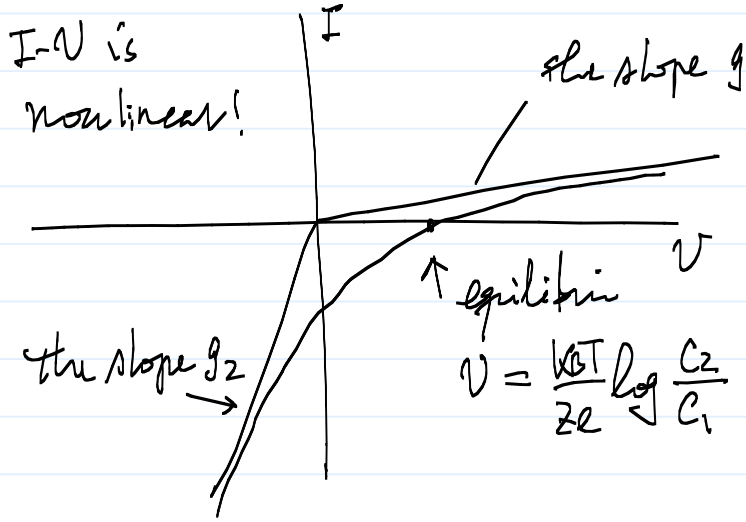
— recovering the Nerst eqn in thermal equilibrium.

If $\frac{ZeV}{k_BT} \gg 1$

$$I \sim \frac{a(Ze)^2 \mu V}{L} C_1 \equiv g_1 V$$

If $\frac{ZeV}{k_BT} \ll 1$ $\quad I \sim \frac{a(Ze)^2 \mu V}{L} C_2 \equiv g_2 V$

The I-V curve for $C_2 > C_1$, $Z > 0$



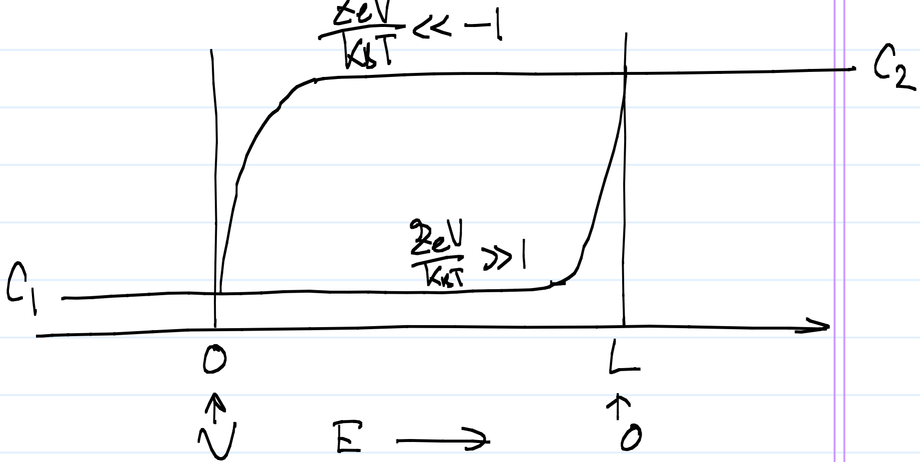
NB: The channel behaves like a rectifier (nonlinear) i.e. it has a larger conductance for current flow in the direction consistent with the diffusion.

— The Distribution of Ions:

Solve for $C(x) \Rightarrow$

(1) if $\frac{ZeV}{k_BT} \ll -1$, $C(x) \sim C_2$

(2) if $\frac{ZeV}{k_BT} \gg 1$, $C(x) \sim C_1$



The notion of Permeability. $\left(P = \frac{aD}{L}\right)$

Def $\theta = \frac{ZeV}{K_BT}$,

rewrite $I \Rightarrow$

$$I = ZeP\theta \cdot \frac{C_1 e^{\theta} - C_2}{e^{\theta} - 1}$$

↑

$$P = \frac{aK_BT\mu}{L} = \frac{a\overset{D = K_BT\mu}{D}}{L}$$

The significance of permeability P

NB $V \to 0$, i.e. $\theta \to 0$ $\because$ $\frac{\theta}{e^{\theta} - 1} \to 1$ as $\theta \to 0$

we have

$$\lim_{\theta \to 0} I = ZeP\cdot(C_1 - C_2) = Ze\cdot a\cdot \overbrace{D\frac{(C_1 - C_2)}{L}}^{-D\frac{\partial c}{\partial x}}$$

↑

an expected formula
from pure diffusion
through channels

The Goldman-Hodgkin-Katz formula.

Consider Mixture of Na^+, K^+, and Cl^- channels

For, Na^+, K^+, $z=+1$, For Cl^-, $z=-1$

$$\therefore \quad \frac{zeV}{k_BT} = \begin{cases} +\theta & \text{for } Na^+, K^+ \\ -\theta & \text{for } Cl^- \end{cases}$$

$$\therefore \quad I_{Na} = eP_{Na}\theta\,\frac{[Na^+]_1e^{\theta}-[Na^+]_2}{e^{\theta}-1}$$

$$I_K = eP_K\theta\,\frac{[K^+]_1e^{\theta}-[K^+]_2}{e^{\theta}-1}$$

$$I_{Cl} = -eP_{Cl}(-\theta)\,\frac{[Cl^-]_1e^{-\theta}-[Cl^-]_2}{e^{-\theta}-1}$$

$$= eP_{Cl}\theta\,\frac{[Cl^-]_2e^{\theta}-[Cl^-]_1}{e^{\theta}-1}$$

NB. the subscript switched.

$$\therefore \quad I = I_{Na}+I_K+I_{Cl}$$

Q: When is the equilibrium?

i.e. $I=0$ Q. What is the corresponding V?

Solve for V from $I=0$ i.e.

$$([Na^+]_1e^{\theta}-[Na^+]_2)P_{Na} + ([K^+]_1e^{\theta}-[K^+]_2)P_K + ([Cl^-]_2e^{\theta}-[Cl^-]_1)P_{Cl} = 0$$

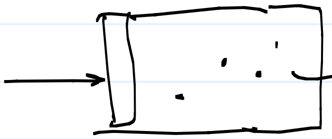
$$\therefore \quad \frac{eV}{k_B T} = \vartheta = \log \frac{P_{Na}[Na^+]_2 + P_K[K^+]_2 + P_{Cl}[Cl^-]_1}{P_{Na}[Na^+]_1 + P_K[K^+]_1 + P_{Cl}[Cl^-]_2}$$

$$\therefore \quad V = \frac{k_B T}{e} \log \frac{P_{Na}[Na^+]_2 + P_K[K^+]_2 + P_{Cl}[Cl^-]_1}{P_{Na}[Na^+]_1 + P_K[K^+]_1 + P_{Cl}[Cl^-]_2}$$

— the Goldman-Hodgkin-Katz formula.
i.e. the membrane potential under the
const. field approximation.

Detour: Equilibrium potential of an ion across the membrane.

Work of Concentration:



# of ions.

$$PV = nk_BT$$

Pressure volume.

$$dW = -P\,dV = -\frac{nk_BT}{V}\,dV$$

$$= \frac{nk_BT}{P}\,dP = nk_BT\,\frac{dC}{C}$$

$$C = \frac{n}{V}, \qquad P = k_BT\,C$$

$$\therefore\ W_{1\to 2} = nk_BT\log\frac{C_2}{C_1}$$

Energy Conservation: $\dot{W}_b = \dot{W}_c + \dot{H}$ — the rate the heat is generated.

the rate at which the battery does the work

work rate due to concentration change

$$\dot{W}_b = V\cdot i$$

$$\dot{W}_c = \dot{n}\,k_BT\log\frac{C_2}{C_1} = \frac{i}{qZ}\cdot k_BT\log\frac{C_2}{C_1}$$

the rate of work done to change the Concentration from C_1 to C_2

$$\dot{H} = r\,i^2$$

resistence

$$\therefore\ Vi = i\,\frac{k_BT}{qZ}\log\frac{C_2}{C_1} + r\,i^2$$

The soln is $i = \frac{1}{r}(V - \mathcal{E})$

with $\mathcal{E} = \frac{K_BT}{zq} \log \frac{c_2}{c_1}$ — equilibrium potential for the ion

NB: $i = 0 \Rightarrow V = \mathcal{E} = \frac{K_BT}{qz} \log \frac{c_2}{c_1}$ i.e. equilibrium. (~~**~~)(**).

Comparing eq (*) and eq (~~**~~). $\Rightarrow$

$$\frac{D}{\mu} = K_BT \quad \text{or} \quad D = K_BT\mu$$ — Einstein's relation

— The Einstein relation is a consequence of energy equipartition theorem.

The motion of particle in the fluid can be captured by

$$m\dot{v} = -\gamma v + \xi$$

noise — bombardment of fluid particles.

friction coefficient eg $\gamma = 6\pi\eta R$.

Noise:

$$\langle \xi \rangle = 0 \qquad \langle \xi(t)\xi(t')\rangle = I_R\,\delta(t-t')$$

uncorrelated in time reflecting fast microscopic collisions.

$$\therefore \quad v(t) = \underset{t=0}{v(0)}\, e^{-\frac{\gamma}{m}t} + \frac{1}{m}\int_0^t e^{-\frac{\gamma}{m}(t-s)} \cdot \xi(s)\,ds$$

average over all possible realization of noise.

$$\langle v(t)\rangle = v(0)e^{-\frac{\gamma}{m}t} + \frac{1}{m}\int_0^t e^{-\frac{\gamma}{m}(t-s)} \cdot \underset{\shortparallel\; 0}{\langle \xi(s)\rangle}\,ds$$

$$= v(0)\,e^{-\frac{\gamma}{m}t}$$

— the mean velocity decays to 0.

$$\langle v^2(t)\rangle = \Big\langle \Big(v(0)\,e^{-\frac{\gamma}{m}t} + \frac{1}{m}\int_0^t e^{-\frac{\gamma}{m}(t-s)}\xi(s)\,ds\Big) \cdot \Big(v(0)\,e^{-\frac{\gamma}{m}t} + \frac{1}{m}\int_0^t e^{-\frac{\gamma}{m}(t-s')}\xi(s')\,ds'\Big)\Big\rangle$$

$$= v(0)e^{-\frac{2\gamma}{m}t} + \frac{1}{m^2}\int_0^t\int_0^{t'} e^{-\frac{\gamma}{m}[(t-s)+(t-s')]}\underbrace{\langle \xi(s)\xi(s')\rangle}_{\| \, I_R\,\delta(s-s')} ds\, ds'$$

(NB: the crossterms vanish due to $\langle\xi\rangle = 0$)

$$= v^2(0)\, e^{-\frac{\gamma}{m}(t-t')} + \frac{I_R}{m^2}\int_0^t e^{\frac{2\gamma}{m}(t-s)}\, ds \qquad \frac{m}{2\gamma}$$

$$= v^2(0)\, e^{-\frac{\gamma}{m}(t-t')} + \frac{I_R}{2\gamma m}\cdot\left(1 - e^{-\frac{2\gamma}{m}t}\right)$$

equilibrium $\Rightarrow$ $t \to \infty$ $\quad \therefore \langle v^2\rangle = \dfrac{I_R}{2\gamma m}$

By the equipartition theorem. $\quad \frac{1}{2}m\langle v^2\rangle = \frac{1}{2}k_BT$

$$\frac{1}{2}m\langle v^2\rangle = \frac{I_R}{2\gamma m}\cdot\frac{1}{2}m = \frac{I_R}{4\gamma} = \frac{1}{2}k_BT$$

$$\therefore I_R = 2\gamma k_BT$$

$$x(t) = \int_0^t v(s)\,ds = v(0)\frac{m}{\gamma}\left(1-e^{-\frac{\gamma}{m}t}\right) + \frac{1}{m}\int_0^t ds\int_0^s d\tau\, e^{-\frac{\gamma}{m}(s-\tau)}\xi(\tau)$$

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

Similarly,

$$\langle x^2(t)\rangle = \frac{I_R}{\gamma^2}\left(t - \frac{m}{\gamma}\left(1-e^{-\frac{\gamma}{m}t}\right)\right)$$

$$D = \frac{k_BT}{m\frac{\gamma}{m}} = \frac{k_BT}{\gamma} = \frac{I}{2\gamma^2}$$

$I_R = 2\gamma k_BT$

for $t \gg \frac{m}{\gamma}$, $\langle x^2(t)\rangle = \frac{I_R}{\gamma^2} t$ — Diffusion

mobility $\mu = \frac{1}{\gamma} \leftarrow$ friction

$$\therefore \; 2D = \frac{I_R}{\gamma^2} = \frac{2\gamma k_B T}{\gamma^2}$$

$$\therefore \; D = \frac{k_B T}{\gamma} = k_B T \cdot \mu$$

— Einstein Relation

To summarize.

$$\langle \xi(t) \rangle = 0$$

$$\langle \xi(t)\xi(t') \rangle = 2\gamma k_B T \, \delta(t-t') = \frac{2 k_B T}{D} \delta(t-t')$$

$$\gamma D = k_B T$$

↳ it's determined by the energy equipartition theorem.

$$\underset{\text{fluctuation}}{\underset{\uparrow}{D}} = k_B T \underset{\text{Dissipation}}{\underset{\uparrow}{\mu}}$$

— a special case of fluctuation-dissipation theorem. (FDT)