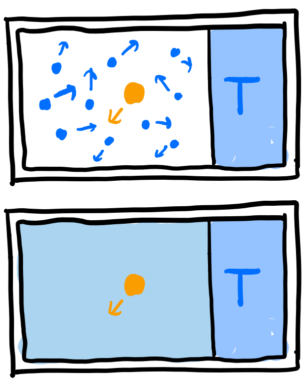
Last time: Brownian Motion / Diffusion



Motion under constant thermal collisions:

$$\Delta v = \underbrace{-\frac{\gamma}{m}\cdot v\cdot\Delta t}_{\text{Effective "Drag"}} + \underbrace{\Delta v_{random}}_{\text{Random "kicks"}}$$

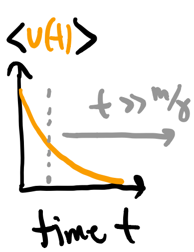
1. Motion of single particle

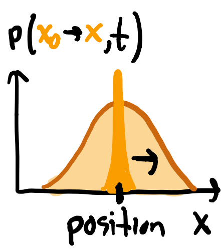
$$p(x_0 \to x, t) \approx \frac{1}{\sqrt{4\pi D t}}\, e^{-\frac{(x-x_0)^2}{4Dt}}$$

↔

2. Diffusion of Concentration

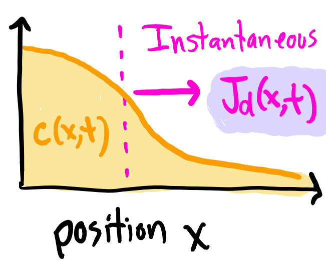
$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left[D\frac{\partial c}{\partial x}\right]$$





Einstein Rel'n

$$D = kT/\gamma$$

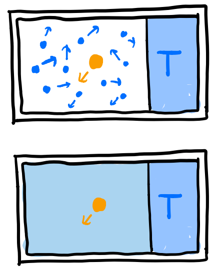


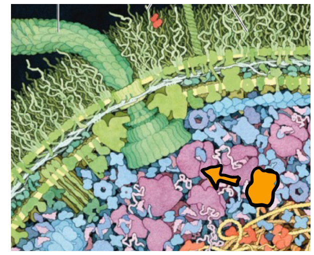
Instantaneous "flux"

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

(particles/time)

* Derived for simple model but dynamics very general!
(must measure γ or D)





* Straightforward to extend to $d=3$ dimensions:

1. Motion of single particle

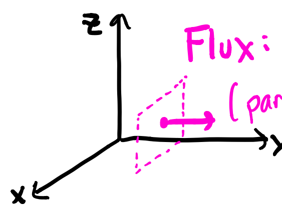
$$p(\vec{x}_0 \to \vec{x}, t) \approx \prod_{i=1}^{d} \frac{e^{-\frac{(x_i - x_{0i})^2}{4Dt}}}{\sqrt{4\pi D t}}$$

Einstein Relation: $\gamma D = kT$

2. Diffusion of Concentration

$$\frac{\partial c}{\partial t} = -\sum_{i=1}^{d} \frac{\partial}{\partial x_i}\Big[\underbrace{-D\frac{\partial c}{\partial x_i}}_{\text{Flux: } J_i(\vec{x},t)}\Big]$$

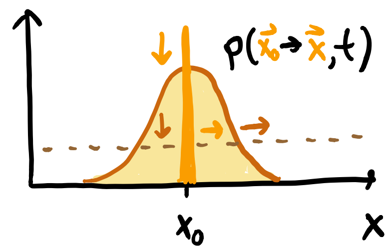
(particles/area/time)



+ **Rotational Diffusion** ($\langle \theta(t)^2 \rangle = 2D_\theta t$), etc.

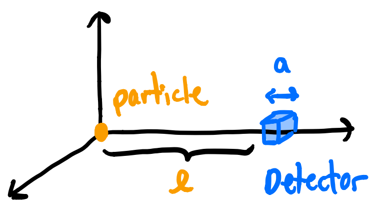
Today: How do we interpret these results?
What constraints do they impose on biology?

Diffusion as concentration equalizer



$\Updownarrow$

Today: diffusion as a transport or signaling process



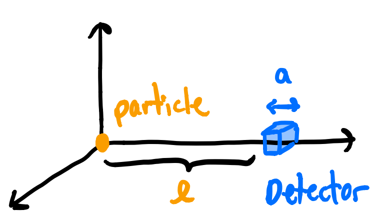
If $a \ll \ell$:

$$P_{detect}(t) \propto a^d \cdot p(\vec{x}_0 \to \vec{x}_0 + \ell\hat{x}, t)$$

$$\Rightarrow \quad P_{detect}(t) = \frac{a^d}{(4\pi D t)^{d/2}}\, e^{-\ell^2/4Dt} \qquad (d=1,2,3)$$

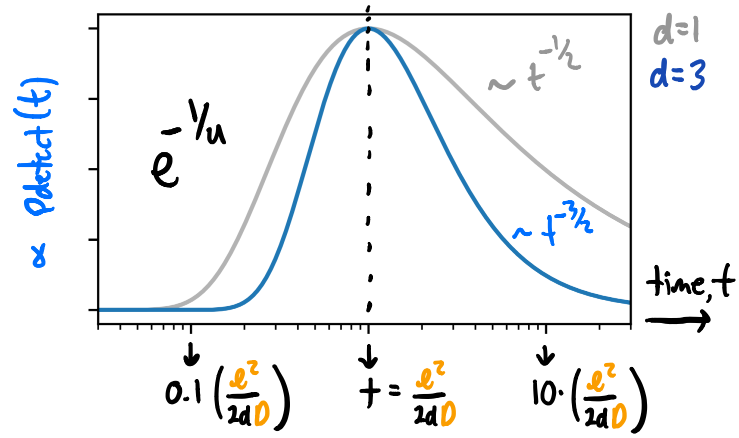
* What does this look like as function of time?

$\Rightarrow$ useful to change variables: $t \equiv \frac{\ell^2}{D} \cdot u$

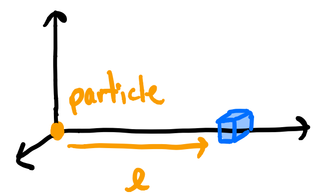


$$P_{detect}\left(t = \frac{\ell^2}{D} u\right) = \left(\frac{a}{\ell}\right)^d \cdot \frac{e^{-1/4u}}{(4\pi u)^{d/2}}$$

"Universal" form :



$\Rightarrow$ Diffusion timescale $\tau_d \equiv \ell^2/D$ required to travel distance ℓ



$\Rightarrow$ increases w/ ℓ (farther distance ✓)

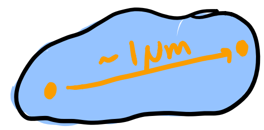
decreases w/ D (faster thermal motion ✓)

$\Rightarrow$ but grows as ℓ^2! [compare to $\Delta t = \ell/v$]

$\Rightarrow$ will lead to some counter-intuitive behavior...

Examples of diffusion timescales: $\tau_d \sim \ell^2/D$

① Diffusion of small molecule (e.g. glucose / ATP) w/in E. coli cell



$\Rightarrow$ measured $D \approx (10\,\mu m)^2/s$

$$\Rightarrow \tau_d = \frac{(1\,\mu m)^2}{(10\,\mu m)^2/s} = 0.01\ s$$

② Diffusion of protein w/in E. coli Cell $[D \approx (3\,\mu m)^2/s]$

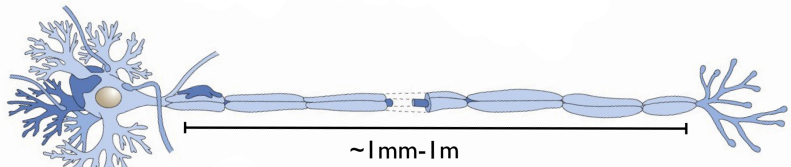
$$\Rightarrow \tau_d = \frac{(1\,\mu m)^2}{(3\,\mu m)^2/s} \approx 0.1\ s$$

$\Rightarrow$ But things change quickly if we increase ℓ...

③ Eukaryotic cells ($\ell \sim 10\,\mu m$) $\Rightarrow$ small molecules: $\tau_d \sim 1s$

proteins: $\tau_d \sim 10s$

④ Extreme case: human motor neuron:



~ 3000yrs!

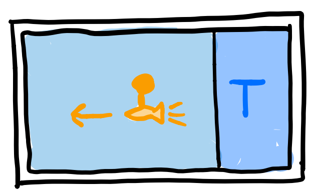
diffusion of protein: $\tau_d = \frac{\ell^2}{D} = \frac{(10^6 \mu m)^2}{(3 \mu m)^2/s} \sim 10^{11} s$!

Problem: most proteins synthesized near nucleus...

$\Rightarrow$ How does cell transport them across axon?

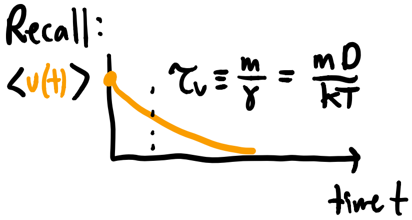
Answer: needs active transport

(i.e. use energy)



$\Rightarrow$ but not so easy in face of thermal noise...

Recall:



$\Rightarrow$ initial velocity lost after distance:

$$\Delta x \sim v_0 \cdot \tau_v \sim v_0 m D / kT$$

$\Rightarrow$ need to replenish velocity ($v=0 \rightarrow v=v_0$) every Δx:

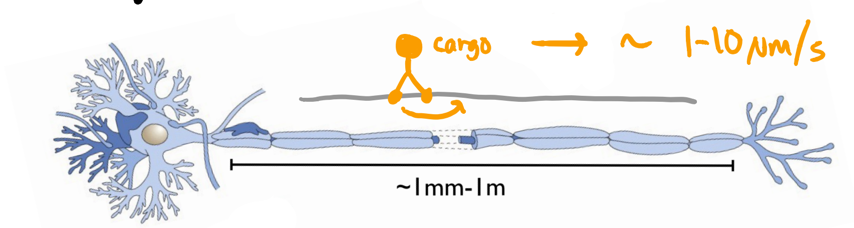
$\Rightarrow$ requires energy $\Delta E = \frac{1}{2} m v_0^2 \sim m v_0^2$

$\Rightarrow$ Energy required per distance:

$$\frac{\Delta E}{\Delta x} \sim \frac{m v_0^2}{v_0 m D / kT} \sim \frac{v_0}{D} \cdot kT \sim \frac{v_0}{200} \text{ ATPs}/\text{distance}$$

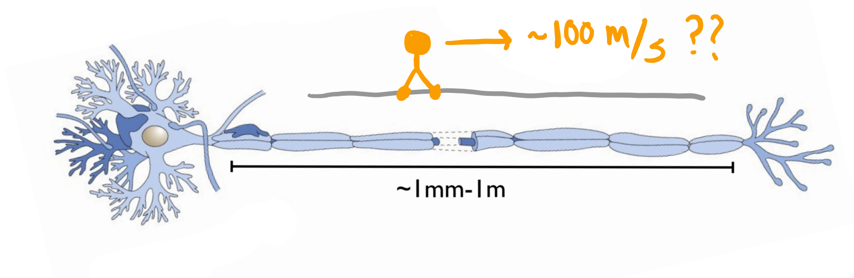
$\Rightarrow$ Energy costs increase w/ v_0

E.g. motor proteins:



$$\Rightarrow \frac{3\,\mu m}{s} = \frac{3\,\cancel{\mu m}}{\cancel{s}} \cdot \frac{1\,cm}{10^4\,\cancel{\mu m}} \cdot \frac{10^5\,\cancel{s}}{day} \sim 30\ cm/day.$$

Question: what if you wanted to send signal as fast as an action potential?



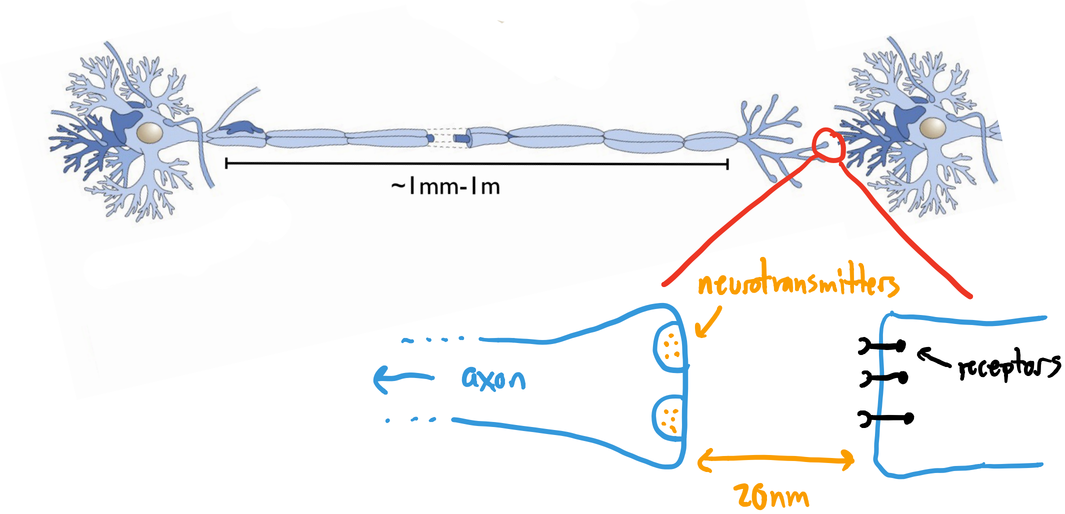
$$\text{total energy required} = \frac{v_0}{200} \cdot \Delta x = \frac{(100\,m/s)(1\,m)}{20 \cdot (3\mu m)^2/s} = 5\times10^{11}\ \text{ATPs}$$

off by ~100x

$\Rightarrow$ But typical cells only contain ~ 5×10^{9} ATPs!

$\Rightarrow$ need some other solution (e.g. bioelectricity)

5 Diffusion of neurotransmitters @ synapses

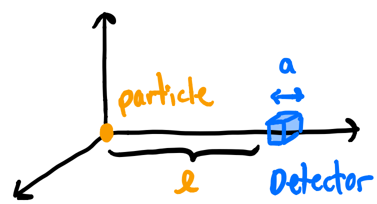


e.g. acetylcholine: $D \sim (20\,\mu m)^2/s$
(small molecule)

$$\Rightarrow \tau_d \sim \frac{\ell^2}{D} \sim \frac{(20\,nm)^2}{(20\,\mu m)^2/s} = \frac{(20\times 10^{-3}\,\mu m)^2}{(20\,\mu m)^2/s} \sim 10^{-6}\,s$$

$\Rightarrow$ actual time is $\sim 10^{-3}$ s... what sets this?

Diffusion-to-capture



so far, focused on time required for signal to travel via diffusion...

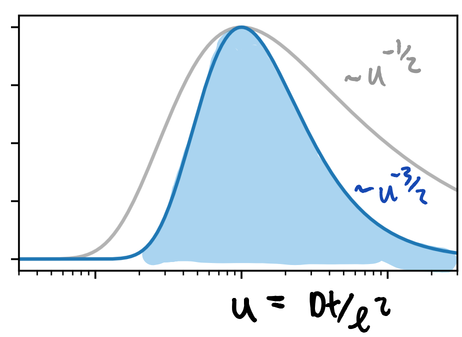
$\Rightarrow$ but physics of diffusion also limits probability that particle is detected ("captured")

#

$$\text{total probability of detection} \propto \int_0^\infty P_{detect}(t)\, dt = \frac{a^d \ell^2}{D} \times \boxed{\int_0^\infty \frac{e^{-1/4u}}{(4\pi u)^{d/2}}\, du}$$

$\Rightarrow$ in 1d: diverges!

$\Rightarrow$ in 3d: finite!

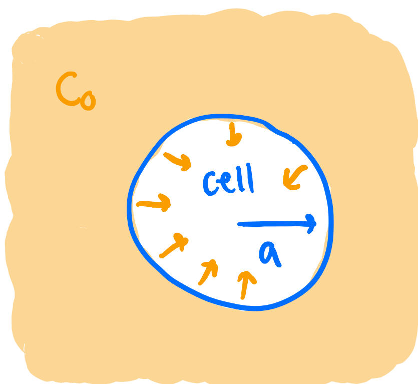


$\Rightarrow$ in 3d, finite chance that particle is never captured!

(exact probability worked out in supplemental note below)

⇒ imposes fundamental limits on rate @ which cells (or other 3d region) can capture particles through diffusion

⇒ can illustrate w/ simple model:

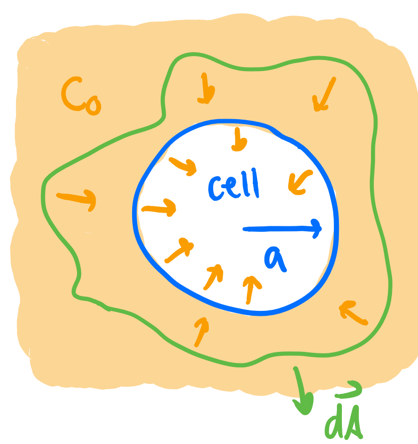


① cell is sphere of radius a

② in concentration field $c(\vec{x}) \to c_0$ $(|\vec{x}| \gg a)$

③ Takes up particles @ total rate R (particles/time)

⇒ by conservation of mass, total particles through any other shape containing cell must also be = R

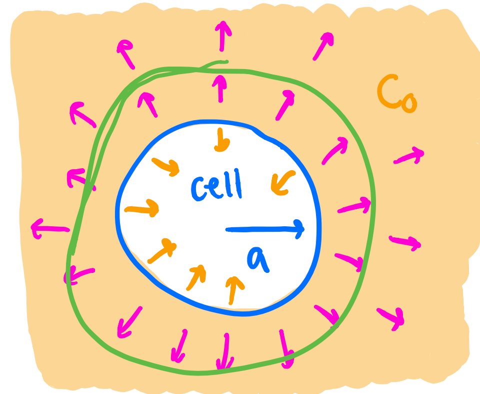


⇒ can express in terms of flux: (particles per area per time)

$$\oint \vec{J}(\vec{x}) \cdot \vec{dA} = -R$$

integrate over surface area

$\Rightarrow$ spherical symmetry implies that $\vec{J}(\vec{x}) = J_r(r)\cdot\hat{r}$



$\Rightarrow$ $4\pi r^2 J_r(r) = -R$

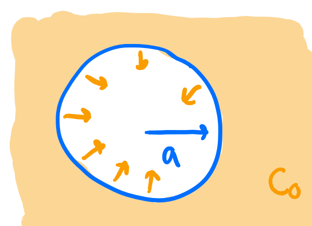
+ Fick's law: $J_r(r) = -D\dfrac{\partial c(r)}{\partial r}$

$$\Rightarrow \frac{\partial c(r)}{\partial r} = \frac{-J_r(r)}{D} = \frac{R}{4\pi D r^2}$$

Solution: $c(r) = \text{const} - \dfrac{R}{4\pi D r} = c_0\left(1 - \dfrac{R}{4\pi D r c_0}\right)$ ✓

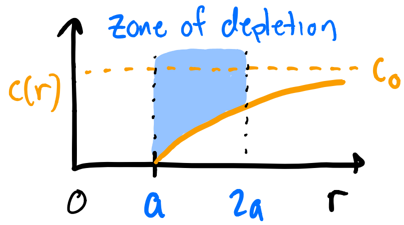
Since $c(r) \geq 0$ for $r \geq a$

$\Rightarrow$ $R \leq R_{max} \equiv 4\pi D a c_0$

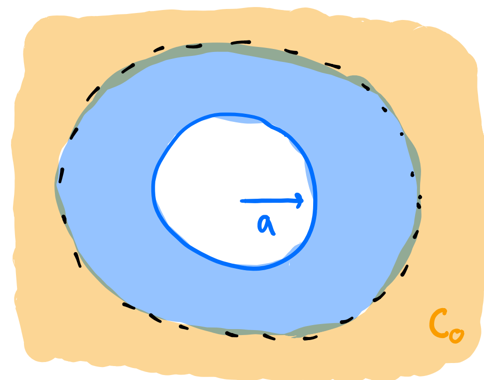


Universal "speed limit" on capture of particles via diffusion in 3d

$\Rightarrow$ @ $R = R_{max}$:



$\Leftrightarrow$



Intuition :

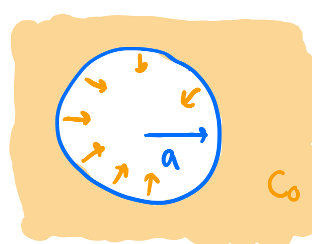
① $\sim c_0 a^3$ particles in depletion zone

② diffusion time $\sim a^2/D$

$$\Rightarrow R_{max} = \frac{\text{particles}}{\text{time}} \sim \frac{c_0 a^3}{a^2/D} \sim D a c_0 \quad \checkmark$$

$\Rightarrow$ increases w/ c_0, D, a

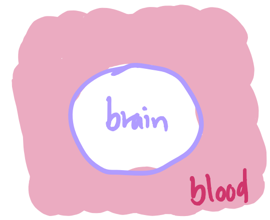
$\Rightarrow$ but scales linearly in a
(as opposed to surface area $\propto a^2$)



Lots of applications...

① Limits on cell size / tissue architecture

<u>Question</u>: could human brain be implemented as single cell w/ same size/shape?



Let's focus on <u>energy</u> <u>requirements</u>:

① Brain needs ~300 calories per day

$$R = \frac{300 \text{ cal}}{\text{day}} \cdot \frac{1 \text{ g sugar}}{4 \text{ cal}} \cdot \frac{1 \text{ day}}{10^5 \text{ s}} \sim 10^{-3} \text{ g sugar/s}$$

② How much can import @ speed limit $R_{max} \sim 4\pi D a c_0$?

① $a \sim 20 \text{ cm}$

② $D_{sugar} \sim (70 \mu m)^2/s \sim 5\times10^{-6} \text{ cm}^2/s$

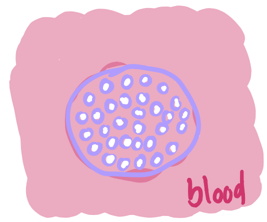
③ Blood: $c_0 \sim \frac{1 \text{ g sugar}}{L} \sim 10^{-3} \text{ g/cm}^3$

$$\Rightarrow R_{max} \sim 4\pi \times (5\times10^{-6} \cancel{\text{cm}^2}/s) \times (20 \cancel{\text{cm}}) \times \left(\frac{10^{-3} \text{ g}}{\cancel{\text{cm}^3}}\right) = 10^{-6} \text{ g sugar/sec.}$$

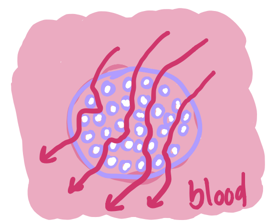
⇒ 3 orders of magnitude too small!

⇒ what do organisms do instead??

⇒ multicellularity?



⇒ need <u>active</u> <u>transport</u>
(e.g. blood circulation)

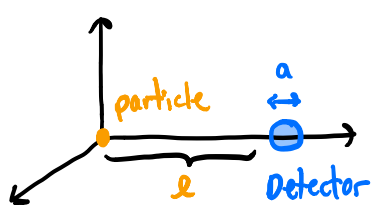


Supplemental Note: Diffusion hitting probability in 3d

To gain intuition for the speed limit $R_{max} = 4\pi D a c_0$,
will be helpful to explicitly calculate probability
that single particle diffuses to region distance ℓ away.

will do this in two ways:

① Integrating $P_{detect}(t)$ over time.

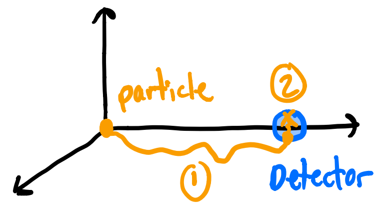


⇒ In limit of low detection rate, we argued above that

$$p(\text{detect}) = \int P_{detect}(t)\,dt \propto \frac{a^3}{D\ell}$$

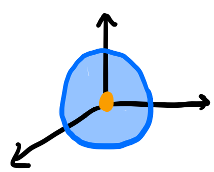
$\Rightarrow$ can break detection into two stages:

1. particle reaches detector region
2. particle is detected after entering detector region



$$\Rightarrow \quad p(\text{detect}) = p\left(\text{detect} \,\middle|\, \substack{\text{reaches} \\ \text{detector}}\right) p\left(\substack{\text{reaches} \\ \text{detector}}\right)$$

$\Rightarrow$ we can calculate by considering related detection problem:



$$p\left(\text{detect} \,\middle|\, \substack{\text{reaches} \\ \text{detector}}\right) \propto \int dx\,dy\,dz\,dt \, \frac{1}{(4\pi D t)^{3/2}} e^{-\frac{x^2+y^2+z^2}{4Dt}}$$

$$\propto \int_0^a 4\pi r^2 dr \int_0^\infty dt \, \frac{1}{(4\pi D t)^{3/2}} e^{-r^2/4Dt}$$

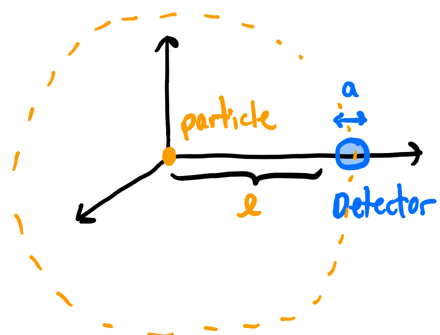
$\Rightarrow$ change of variables: $r = av$, $t = \frac{a^2}{D} u$

$$p\left(\text{detect}\,\middle|\,\substack{\text{reaches}\\ \text{detector}}\right) \propto \frac{a^2}{D} \cdot \Bigg[\underbrace{\int_0^1 4\pi v^2 dv \int_0^\infty \frac{du}{(4\pi u)^{3/2}} e^{-v^2/4u}}_{\text{just a constant}} \Bigg]$$

Combining these results, we have:

$$p\left(\substack{\text{reaches}\\ \text{detector}}\right) \propto \frac{p(\text{detect})}{p\left(\text{detect}\,\middle|\,\substack{\text{reaches}\\ \text{detector}}\right)} \propto \frac{\frac{a^3}{D\ell}}{a^2/D} \propto \frac{a}{\ell}$$

$\Rightarrow$ **Hitting probability $\propto \frac{a}{\ell}$**

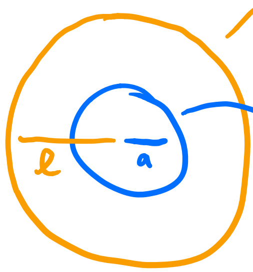


Note: scales like ratio of
linear dimensions (a, ℓ)
rather than ratio of surface areas ($\propto a^2, \ell^2$)

② Solving diffusion equation

we can also derive this result exactly using a variant of the "Gauss's law" approach we used to calculate $R_{max} = 4\pi D a c_0$ ...

Basic setup:



① "Shell" providing constant source of particles @ rate R_0 (particles/time)

② cell absorbing particles @ rate R (particles/time)

③ No concentration maintained @ $r=\infty$

Solution: $p(\text{captured}) \equiv \frac{R}{R_0} \leq \frac{R_{max}}{R_0} = \frac{a}{\ell}$

(excercise for reader – Hint: consider flux through spheres inside + outside shell)

Heuristic derivation of limit to capture rate

$\Rightarrow$ we can use the hitting probability above to obtain a "heuristic" derivation of $R_{max} \sim D a c_0$

(valid in the limit of low concentrations)

① A volume of radius ℓ contains $\sim c_0 \ell^3$ particles

$\Rightarrow$ closest particle to detector has $\ell^* \sim c_0^{-1/3}$

② This particle has probability $\sim a/\ell^*$ of hitting our detector

③ Will reach detector on timescale $\sim {\ell^*}^2/D$

$$\Rightarrow \quad R_{max} \sim \frac{1 \text{ particle} \cdot a/\ell^*}{{\ell^*}^2/D} \sim \frac{Da}{{\ell^*}^3} \sim D a c_0 \quad \checkmark$$

$\Rightarrow$ shows that linear scaling of R_{max} emerges from linear scaling of hitting probability in 3D

⇒ technically, this argument only applies for short times...

⇒ @ longer times, total # of captured particles is

$$N(t) \sim \int_0^{\mathcal{O}(\sqrt{Dt})} \underbrace{4\pi r^2 dr \cdot c_0}_{\substack{\text{total \# of particles} \\ \text{in shell @ distance } r}} \cdot \underbrace{\frac{a}{r}}_{\substack{\text{probability that} \\ \text{reaches detector}}}$$

maximum radius that can reach detector in time t

$$\Rightarrow R_{max} \approx \frac{N(t)}{t} \sim \frac{D \cdot a \cdot c_0 \cdot t}{t} \sim D \cdot a \cdot c_0 \quad \checkmark$$

⇒ this argument shows why limits on capture rate only exist for $d \geq 3$

[Hint: try setting $p_{hit} = 1$ in integral above]

Limits to capture rate via dimensional analysis

we can also obtain the maximum capture rate almost "for free" using dimensional analysis.

⇒ capture rate R has units of particles/time.

⇒ if a maximum capture rate exists,
we know it can only depend on:

1. detector size a [units: length]
2. diffusion constant D [units: length^2/time]
3. external concentration c_0 [units: particles/length^3]

⇒ the only way to combine these 3 quantities to obtain same units as R is $R_{max} \propto D \cdot a \cdot c_0$ ✓

⇒ shows that linear scaling in a is tied to length^2 units of diffusion constant D

⇒ however, this argument doesn't give much insight into the role of 3D space.

⇒ e.g. same dimensional analysis can be done for $d=1,2$:

⇒ $d=1$: $R_{max} \propto Dc_0/a$ / $d=2$: $R_{max} \propto Dc_0$

⇒ but in both cases we know that $R_{max} = \infty$!

⇒ shows that existance of finite R_{max} was crucial assumption, which is hard to obtain from dimensional analysis alone...