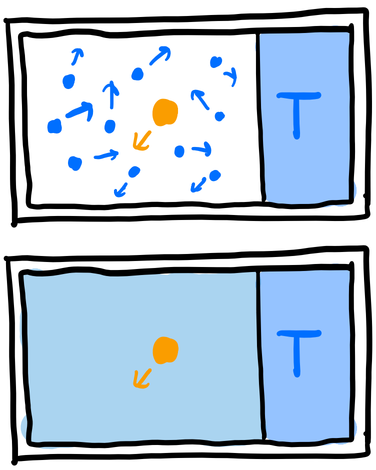
Announcements

1. Advance copy of notes on Canvas
2. Common question: velocity "memory"? → Supplemental note 2 in Lecture 4
3. Supplemental Reading: Purcell, "Life @ low Reynolds #"

Last time: Brownian Motion / Diffusion



Motion under constant thermal collisions:

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

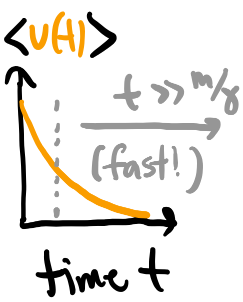
1. Motion of single particle

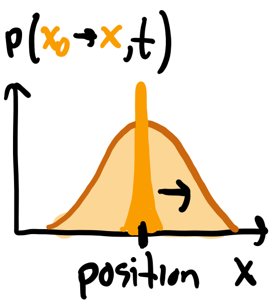
$$p(x_0 \to x, t) \approx \frac{1}{\sqrt{4\pi D t}}\, e^{-\frac{(x-x_0)^2}{4Dt}}$$

↔

2. Diffusion of Concentration

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

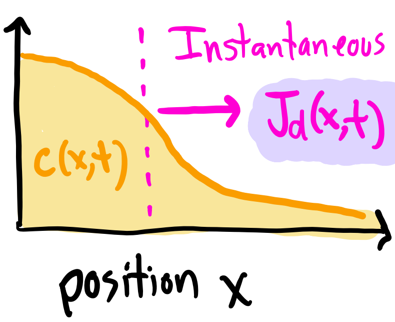




Einstein Rel'n

$$\boxed{D = kT/\gamma}$$

**

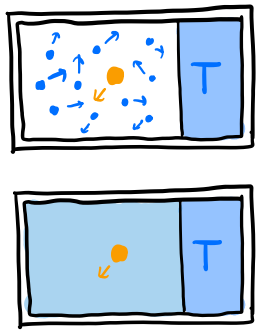


Instantaneous "flux"

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

(particles/time)

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



e.g. Stokes law: $\gamma = 6\pi\eta a$

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

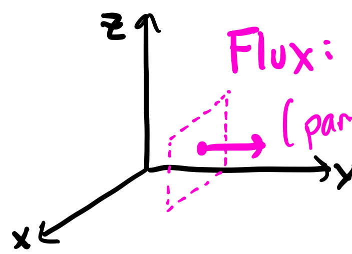
1. Motion of single particle

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

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)

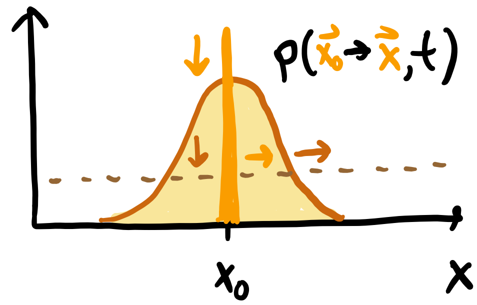


Einstein Relation: $\gamma D = kT$

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

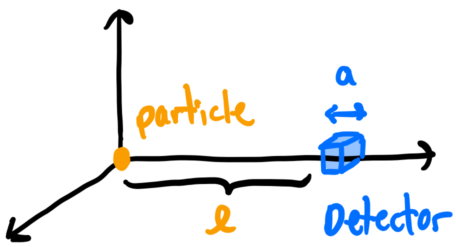
Today: How do we interpret these results?
What constraints do they impose on biology?

Diffusion as concentration equalizer



$\Updownarrow$

Today: diffusion as a transport or signaling process



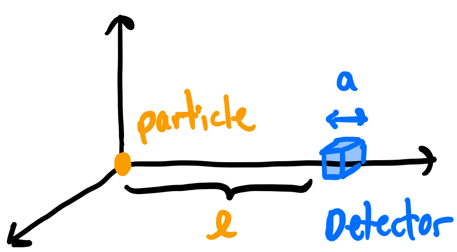
If $a \ll \ell$:

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

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

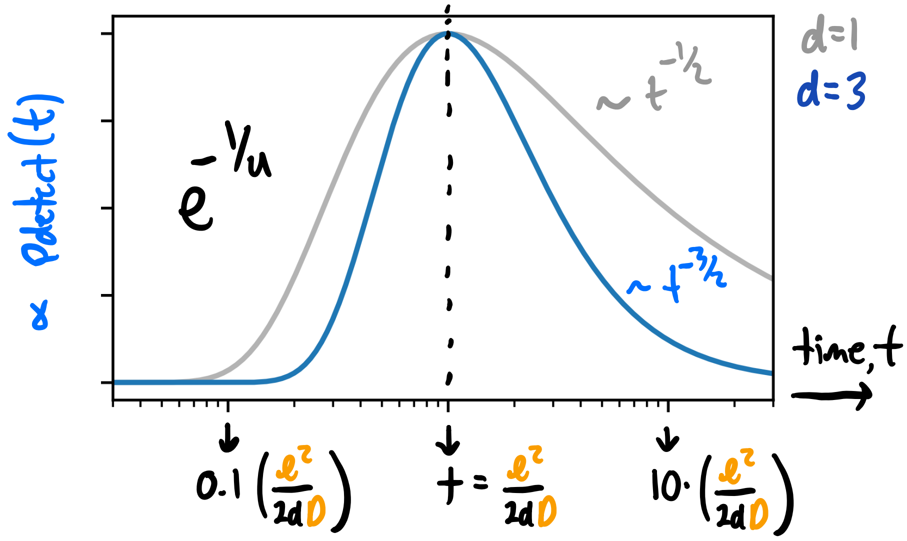
* What does this look like as function of time?

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

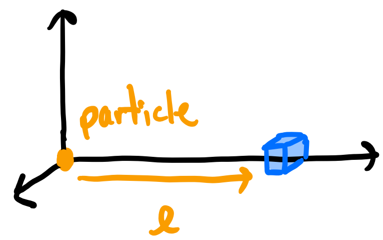


$$P_{detect}\left(t = \frac{\ell^2}{D} u\right) = \left(\frac{a}{\ell}\right)^d \cdot \frac{e^{-1/4u}}{(4\pi u)^{d/2}}$$

"Universal" form:



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



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

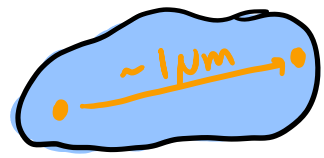
decreases w/ D (faster thermal motion ✓)

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

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

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

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

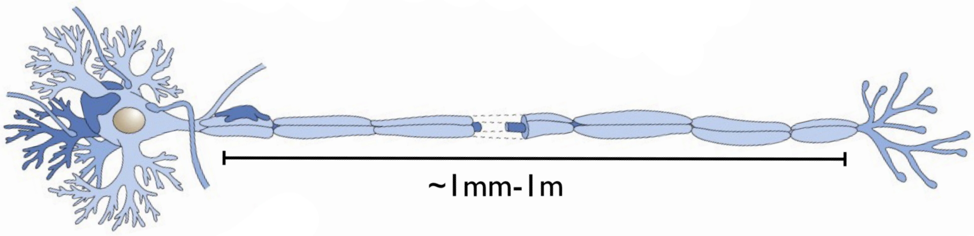
$\Rightarrow$ But things change quickly if we increase ℓ...

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

proteins: $\tau_d \sim 10s$

* exercise *

④ Extreme case: human motor neuron:



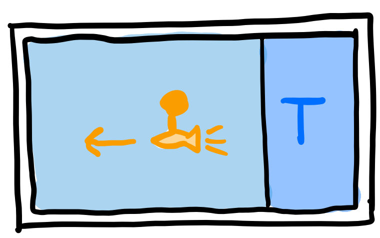
diffusion of protein: $\tau_d = \frac{\ell^2}{D} = \frac{(10^6\,\mu m)^2}{(3\,\mu m)^2/s} \sim 10^{11}\,s\,!$ → 3000 yrs.

<u>Problem</u>: all mRNA is transcribed near nucleus (instructions for making protein)

$\Rightarrow$ How does cell make proteins throughout axon?

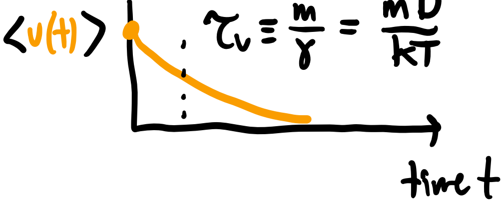
<u>Answer</u>: needs <u>active</u> <u>transport</u>

(i.e. use energy)



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

Recall: $\tau_v \equiv \frac{m}{\gamma} = \frac{mD}{kT}$



$\Rightarrow$ initial velocity forgotten after distance:

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

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

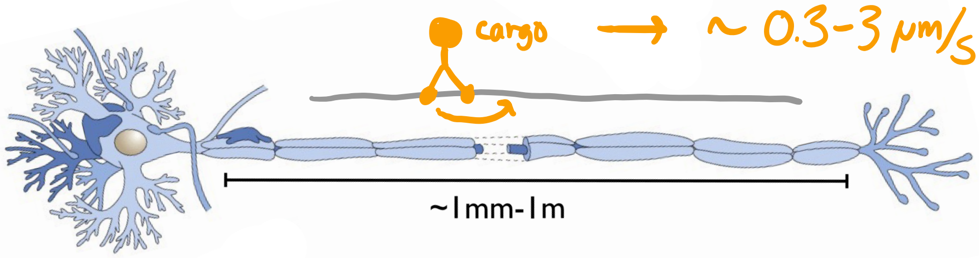
$\Rightarrow$ requires energy $\Delta E = \frac{1}{2} m v_0^2 \sim m v_0^2$

$\Rightarrow$ Energy required per distance:

$$\frac{\Delta E}{\Delta x} \sim \frac{\cancel{m} v_0^{\cancel{2}}}{\cancel{v_0} \cancel{m} D / kT} = \frac{v_0 kT}{D} = \frac{v_0}{D} \frac{(\cancel{20kT})^{\text{1 ATP}}}{20} = \frac{v_0}{20D} \ \frac{\text{ATPs}}{\text{distance}}$$

$\Rightarrow$ Energy costs increase w/ v_0!

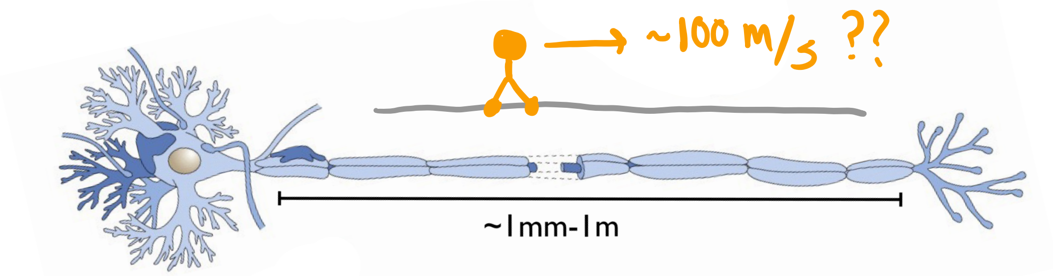
E.g. motor proteins:



Further reading: see Ch. 16 of Phys. Biol. of Cell!

$$\Rightarrow \frac{3\,\mu m}{s} = \cancel{300}\,\frac{3\,\mu m}{s} \times \frac{1\,cm}{10^4\,\mu m} \times \frac{10^5\,s}{1\,day} = 30\,cm/day$$

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



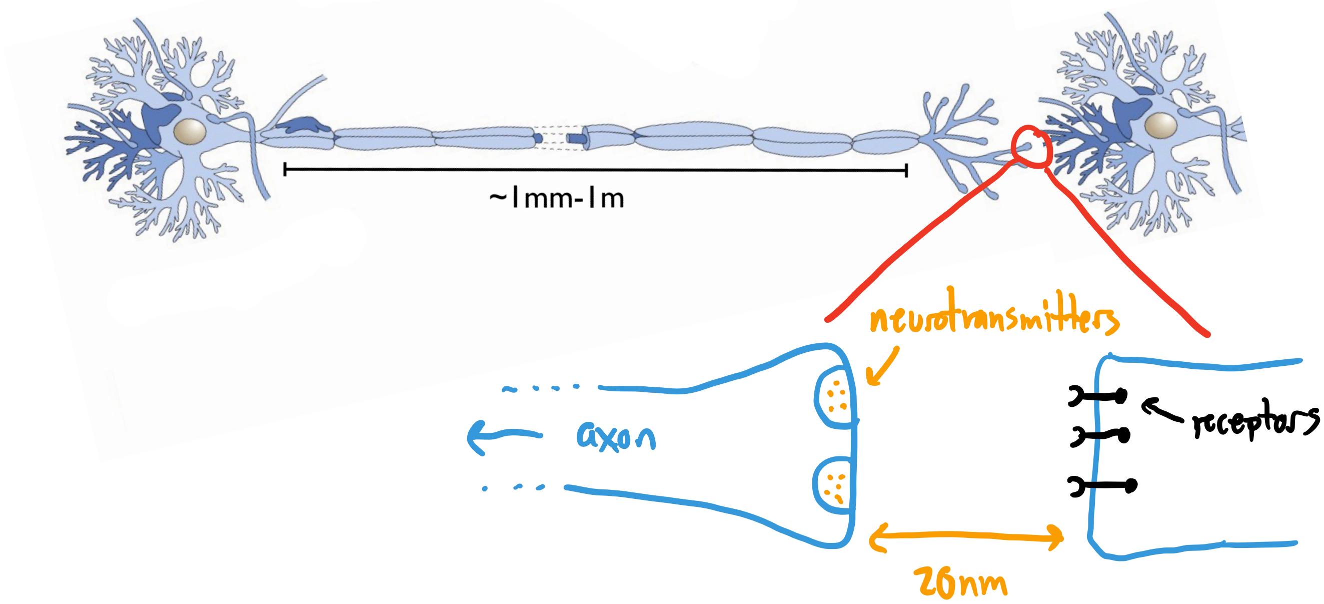
$$\text{total ATP required} = \frac{v_0}{20 \cdot D} \cdot \Delta x = \frac{(100\ \mathrm{m/s}) \times (1\ \mathrm{m})}{20 \cdot (3\ \mu\mathrm{m})^2/\mathrm{s}} = 5 \times 10^{11}\ \text{ATPs}$$

100x

⇒ **But** typical cells only contain ~ 5×10^9 ATPs!

⇒ **need** some other solution (e.g. bioelectricity)

(5) Diffusion of neurotransmitters @ synapses

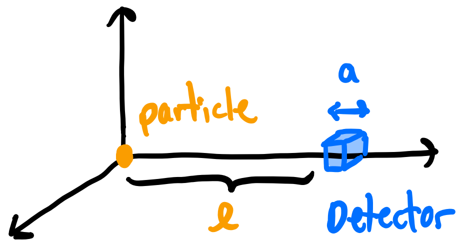


e.g. acetylcholine: $D \sim (20\,\mu m)^2/s$
(small molecule)

$$\Rightarrow \tau_d \sim \frac{\ell^2}{D} \sim \frac{(20\,nm)^2}{(20\,\mu m)^2/s} = \left(\frac{1}{1000}\right)^2 s = 10^{-6}\,s$$

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

Diffusion-to-capture



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

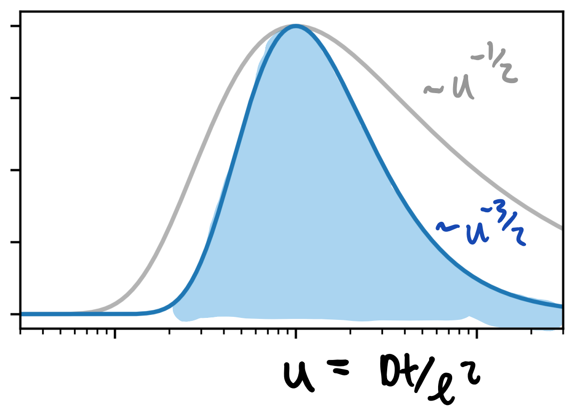
⇒ but physics of diffusion also limits probability that particle is detected ("captured")

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

depends on d.

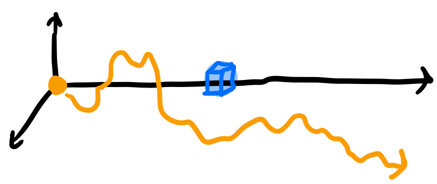
In 1-d: integral diverges $\left(\int_0^\infty \frac{du}{u^{1/2}}\right)$

In 3-d: integral converges to finite # $\left(\int_0^\infty \frac{du}{u^{3/2}}\right)$



⇒ in 3d, finite chance that particle is never captured!

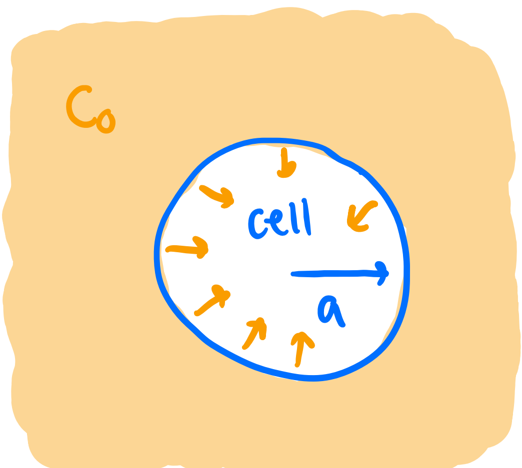
(exact probability worked out in supplemental note below)



$P_{capture} \sim a/\ell$

$\Rightarrow$ imposes fundamental limits on <u>rate</u> @ which cells (or other 3d region) can capture particles through diffusion

$\Rightarrow$ can illustrate w/ simple model:

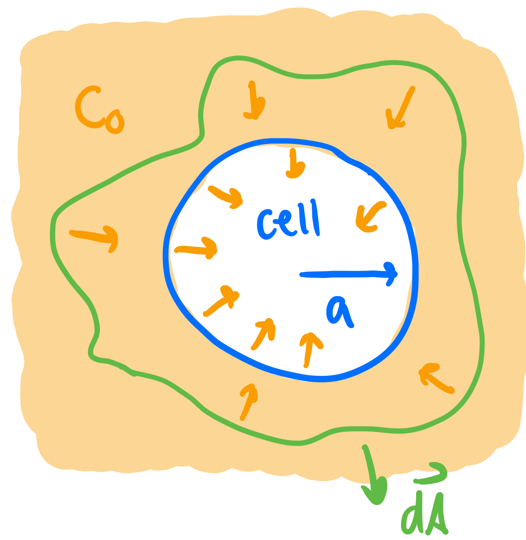


① cell is sphere of radius a

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

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

$\Rightarrow$ by <u>conservation of mass</u>, total particles through any other shape containing cell must also be $= R$

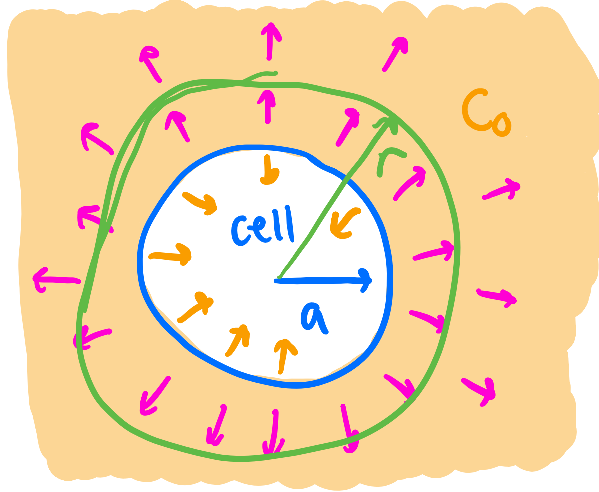


$\Rightarrow$ can express in terms of <u>flux</u>: (particles per area per time)

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

integrate over surface area

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



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

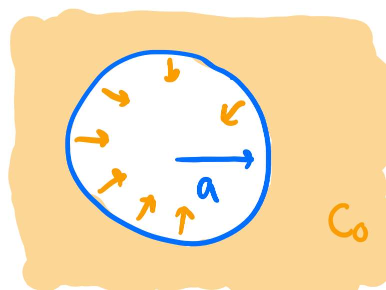
$+$ Fick's law: $J_r(r) = -D\dfrac{\partial c(r)}{\partial r}$

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

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

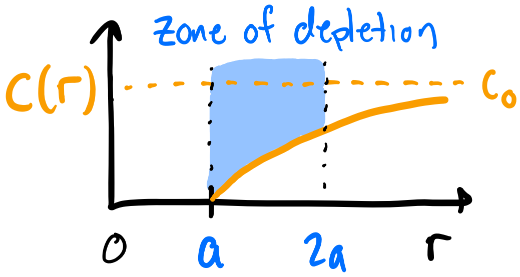
Since $c(r) \geq 0$ for $r \geq a$

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

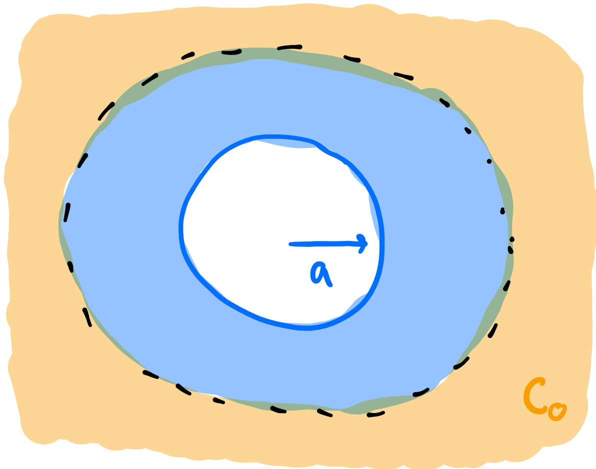


Universal "speed limit" on capture of particles via diffusion in 3d

$\Rightarrow$ when $R = R_{max}$, $c(r) = c_0\left(1 - \frac{a}{r}\right)$



$\Leftrightarrow$



Intuition:

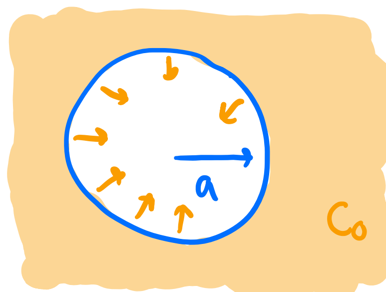
① $\sim c_0 a^3$ particles in depletion zone

② diffusion time $\sim a^2/D$

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

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

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

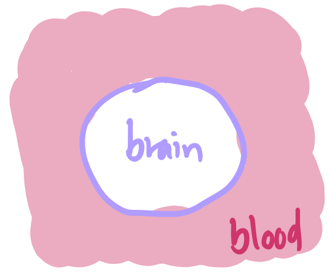


2 alternative derivations in supplemental notes...

$\Rightarrow$ 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

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

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

① $a \sim 20\,\text{cm}$

② $D_{sugar} \sim \frac{(20\,\mu\text{m})^2}{\text{s}} \simeq 5\times10^{-6}\ \text{cm}^2/\text{s}$

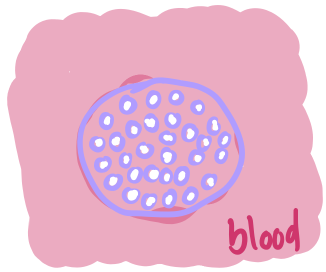
③ Blood: $c_0 \sim \frac{1\,\text{g sugar}}{\text{L}} \sim 10^{-3}\ \text{g}/\text{cm}^3$

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

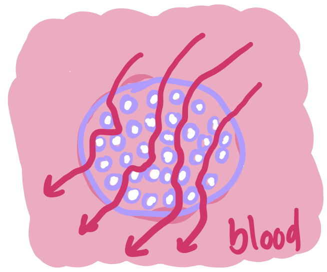
⇒ 3 orders of magnitude too small!

⇒ what do organisms do instead??

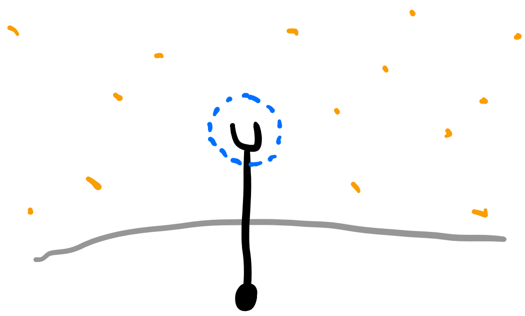
⇒ multicellularity?



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



② Speed limits on rates of chemical reactions



$\Rightarrow$ $a \sim \mathcal{O}(\text{nm})$ (~ small molecule)

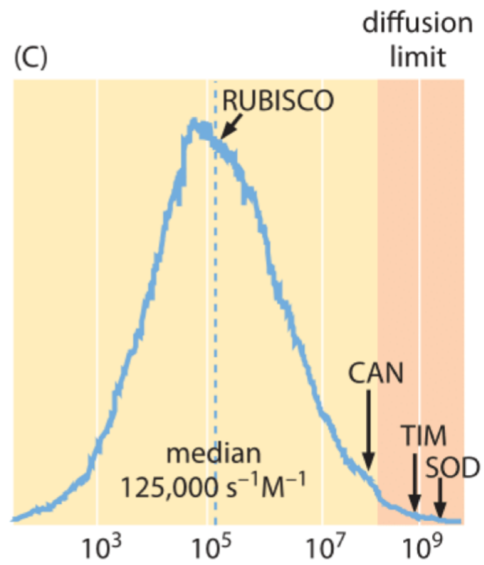
$\Rightarrow$ $D \sim (10\,\mu\text{m})^2/\text{s}$ (~ sugar)

$\Rightarrow$ e.g. $c_0 \sim \dfrac{1\,\text{mole}}{L}$ ("standard conditions")

$$\Rightarrow \quad R_{max} = 4\pi \cdot \left(10^{-6}\,\text{cm}^2/\text{s}\right)\left(10^{-7}\,\text{cm}\right)\left(\frac{6\times10^{23}}{1000\,\text{cm}^3}\right) \sim 6\times10^{8}/\text{s}$$

measured Rates of enzymes:

\# enzymes



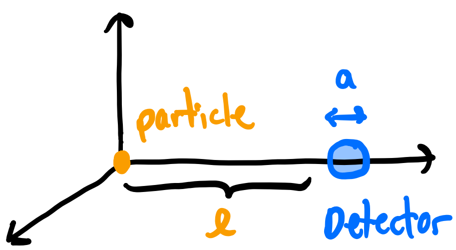
Rate $(s^{-1} \cdot M^{-1})$

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.



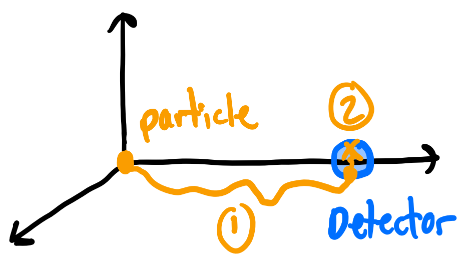
⇒ In limit of low detection rate, we argued above that

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

⇒ can break detection into two stages:

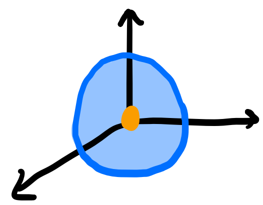
① particle reaches detector region

② particle is detected after entering detector region



$$\Rightarrow\ p(\text{detect}) = p(\text{detect} \mid \text{reaches detector})\, p(\text{reaches detector})$$

⇒ we can calculate by considering related detection problem:



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

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

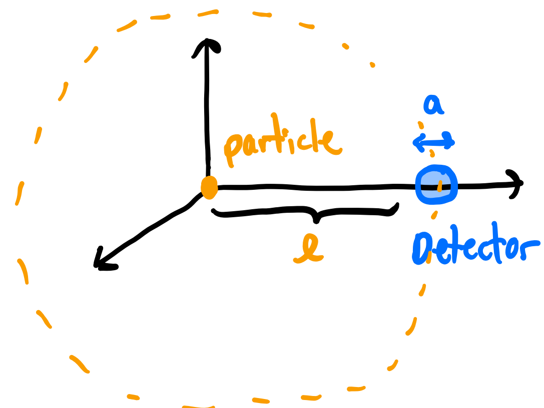
⇒ change of variables: $r = av$, $t = \frac{a^2}{D} u$

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

Combining these results, we have:

$$p(\text{reaches detector}) \propto \frac{p(\text{detect})}{p(\text{detect} \mid \text{reaches detector})} \propto \frac{\frac{a^3}{D\ell}}{a^2/D} \propto \frac{a}{\ell}$$

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

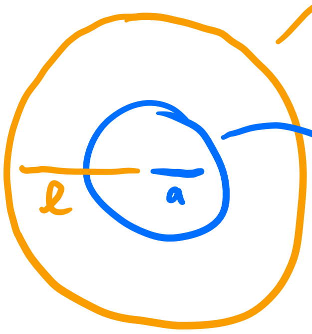


Note: scales like ratio of <u>linear dimensions</u> (a, ℓ) rather than ratio of <u>surface areas</u> $(\propto a^2, \ell^2)$

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

maximum radius that can reach detector in time t

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

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

⇒ 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 <u>dimensional</u> <u>analysis</u>

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 $d=1,2$:

⇒ $d=1$: $R_{max} \propto D c_0 / a$ / $d=2$: $R_{max} \propto D c_0$

⇒ 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...